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HEREDITARY CORNEAL DYSTROPHY

HISTORY OF THE CONDITION AND PRESENTATION OF A PEDIGREE

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A family has recently been observed of which the members presented hereditary corneal dystrophy, a condition to which attention should be called because of its relative rarity and because of the slight variation which new pedigrees add to existing knowledge of it.

HISTORY

A hereditary type of corneal dystrophy, or "nodular corneal opacities," was first described by Groenouw,[1] in 1890. His accurate, lucid and complete observations on 2 patients, not related to each other, left little to be added to the description of this disease. He erred, however, in that he gave a composite picture of the lesions in the 2 cases, for he did not realize that he was dealing with two separate clinical entities. In his composite description, both corneas were affected with numerous sharply defined gray opacities less than 0.25 mm. in diameter. The opacities were closely placed, discrete and separated by healthy corneal stroma. Between these larger opacities, there were countless dustlike gray spots. The affected region occupied exclusively the central area of the cornea and involved the superficial layers. The larger opacities produced small prominences on the surface of the cornea and in this way impaired the visual acuity. The remainder of the cornea was smooth; "epithelial defects do not belong to this disease." The opacities were firm and more resistant to abrasion than the epithelium. They developed slowly and appeared not to extend beyond a certain boundary. They did not show any spontaneous regression and remained stationary for many years. In 1917 Groenouw,[2] having traced the condition through

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1. Groenouw: Knötchenförmige Hornhauttrübungen (Noduli corneae), Arch. f. Augenh. **21**:281-289, 1890.

2. Groenouw: Knötchenförmige Hornhauttrübungen vererbt durch drei Generationen, Klin. Monatsbl. f. Augenh. **58**:411-420, 1917.

three generations in the family of his first patient, was able to present 5 cases. He then also observed that the process was slowly progressive, that by fusion of several opacities irregular figures occurred and that in the course of years fresh spots continued to form. In 1933 his [3] series of cases extended through four generations, and the persons affected included 1 male, the ancestor, and 7 females. He stated that the heredity was dominant.

Since Groenouw's first description, there have been many reports of similar cases of degeneration of the cornea, varying in certain details and having a variety of names attached to them. Biber [4] in 1890, Haab [5] in 1899 and Dimmer [6] in 1899 described a degenerative condition of the cornea under the name of *gittrige Hornhauttrübungen*, or lattice-like corneal opacities. It was left to E. Fuchs,[7] in 1902, to call attention to the similarity of this lattice-like type to Groenouw's nodular variety. Again, in 1905, Doyne and Stephenson [8] described bilateral central degeneration in three generations of a family. They noted the two varieties in different members of the same family and considered them as merely different manifestations of the same process. Sometime later, Fleischer [9] added still a third variety, the so-called ringlike type of corneal degeneration, and noted that the nodular disease was inclined to form the ringlike type by fusion of the individual lesions. Bachstez [10] in 1919 noted still another type of corneal dystrophy, which he described as *Faserfilz,* or meshlike corneal cloudiness, in a mother and son. The boy had suffered since the age of 4 years from numerous attacks of ocular inflammation, especially in the winter. Bachstez was able to observe these attacks, which lasted one or more days and during which the cornea became uneven and the threadlike opacities increased in density. During remissions the cornea was perfectly smooth.

In perusing the literature one finds numerous references to this fascinating condition, which etiologically has aroused much controversy.

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3. Groenouw: Knötchenförmige Hornhauttrübungen, vererbt durch vier Generationen, Klin. Monatsbl. f. Augenh. **90**:577-580, 1933.

4. Biber, H.: Ueber einige seltenere Hornhautterkrankungen: IV. "Die oberflächlichte gittrige Keratitis," Thesis, Zurich, A. Digglemann, Uster, 1890, pp. 35-42.

5. Haab: Die gittrige Keratitis, Ztschr. f. Augenh. **2**:235-246, 1899.

6. Dimmer: Ueber oberflächliche gittrige Hornhauttrübung, Ztschr. f. Augenh. **2**:254, 1899.

7. Fuchs, E.: Ueber knötchenförmige Hornhauttrübung, Arch. f. Ophth. **53**:423-438, 1902.

8. Doyne, R. W., and Stephenson, S.: On Five Cases of Family Degeneration of the Cornea, Ophthalmoscope **3**:213, 1905.

9. Fleischer, B.: Ueber familiäre Hornhautentartung, Arch. f. Augenh. **53**:263-344, 1905; Ueber eine eigenartige, bisher nicht bekannte Hornhauttrübung (Ein Hinweis auf die normale Struktur der Hornhaut), Arch. f. Ophth. **77**:136-140, 1910.

10. Bachstez: Ueber eine neue Form familiärer Hornhautentartung, Klin. Monatsbl. f. Augenh. **63**:387-397, 1919.

Among them is Gutzeit's [11] report of the alternate occurrence of the nodular and the reticular type of degeneration in the same family. Another is that of Jacqueau,[12] who observed a family of 8 members, all of whom suffered with the disease. Frykholm [13] recorded an instance in which the condition extended through six generations, involving 42 members of the pedigree and affecting males and females equally. He also stated that the younger members showed lattice-like, or reticular, opacities, while the older members presented the nodular variety.

Other genealogic studies have appeared sporadically in the literature, presenting cases fundamentally similar to the ones previously reported but differing in one or more manifestations.

The latest and most exhaustive study on the subject of hereditary corneal opacities was published by Bücklers [14] in 1938. He pointed out that two schools of thought had existed up to his time, namely, that of E. Fuchs,[15] who believed that probably various diseases could simulate and be mistaken for the nodular corneal opacities, and that of Fleischer [9] and Collins,[16] who regarded all described cases of hereditary corneal opacity as instances of one disease. Bücklers [14] stated that both were incorrect and showed in his work that all known cases of hereditary corneal dystrophy reported to date could be separated into instances of three distinct, well defined, independent disease entities. These are the crumblike, the macular and the lattice-like corneal dystrophy. Bücklers found 129 cases among 800 members of the families which he investigated in the Württemberg district of Germany. Of these, 91 were of the crumblike type, 32 of the macular type and 6 of the lattice-like type.

These hereditary corneal dystrophies (called homochrone because they are not present at birth) differ from all other types of corneal opacities by being always bilateral, avascular and progressive. In addition to being hereditary, the lesions in a given pedigree show primarily the same tendencies.

Bücklers further noted that the first type, the crumblike corneal dystrophy, or dystrophia corneae granulosa (fig. 1 *A*), was inherited as a mendelian dominant characteristic. He observed that the lesions

11. Gutzeit, R.: Ueber familiäre knötchenförmige Hornhauttrübung, Ztschr. f. Augenh. **68**:349-353, 1929.

12. Jacqueau, L.: Une forme de kératite héréditaire et familiale, Clin. opht. **15**:434-440, 1909.

13. Frykholm, R.: Familiäre Hornhautentartung vererbt durch sechs Generationen, Klin. Monatsbl. f. Augenh. **94**:76-81, 1935.

14. Bücklers, M.: Die erblichen Hornhautdystrophien. Dystrophiae corneae hereditariae, Bücherei des Augenarztes, Stuttgart, Ferdinand Enke, 1938, no. 3.

15. Fuchs, E.: Ueber Knötchenförmige Hornhauttrübung, Arch. f. Ophth. **89**: 337-349, 1914-1915.

16. Collins, E. T.: Hereditary Ocular Degenerations; Ophthalmic Abiotrophies, Tr. Internat. Cong. Ophth., 1922, pp. 103-108; A Case Presenting an Unusual Form of Opacity in the Central Part of Each Cornea, Tr. Ophth. Soc. U. Kingdom **22**:148-150, 1902; Unusual Form of Opacity of Cornea, ibid. **19**:30, 1899.

began in the first decade but were then only visible on biomicroscopy. They increased later in life and took the form of crumbs, rings, crescents and stripes, white in color and glassy in structure. They were situated mainly in the neighborhood of Bowman's membrane and later, also in the deeper layers of the corneal stroma. The cornea between affected areas and in a zone 2 to 3 mm. broad at the periphery always remained clear. Only later in life did the visual acuity perceptibly diminish. The surface became somewhat irregular and the sensibility centrally diminished.

The second type, the macular corneal dystrophy, or dystrophia corneae maculosa (fig. 1 *B*), showed recessive inheritance. This type also made its appearance in the first ten years of life, in the form of a

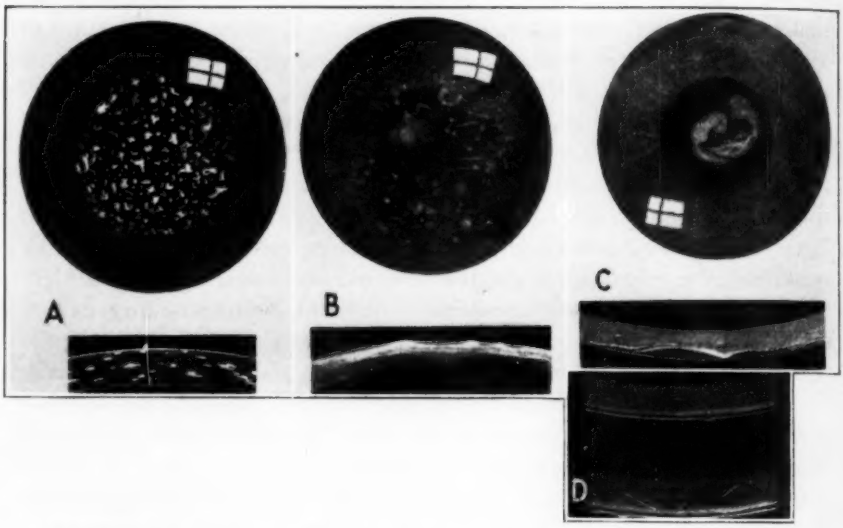

Fig. 1.—Bücklers' three types of hereditary corneal dystrophy (reproduced from drawings in Bücklers' monograph [14]; surface and slit lamp views. *A*, crumb-like; *B*, macular; *C*, lattice-like. *D*, slit lamp view demonstrating canals (clefts, or hyaline bars) and glassy nodules in the lattice-like type.

more or less diffuse and rapidly progressive clouding of the entire cornea. At the age of 20 to 30 the changes were visible macroscopically, and in the central area of the cornea they aggregated into asymmetric gray-white spots in numerous forms. Centrally they were situated superficially and beneath Bowman's membrane, while peripherally they were almost exclusively in the corneal stroma. Unlike the first type, the disease involved the periphery and the area of the cornea between the gray-white spots. The visual acuity was affected in youth and was greatly curtailed in maturity. The epithelium appeared lustrous but irregular and often was crossed by pigment lines. The corneal stroma was greatly thinned and the sensibility markedly diminished.

The third type, the lattice-like corneal dystrophy, or dystrophia corneae reticulata (fig. 1 *C*), like the first type, showed dominant inheritance. It also occurred in the first ten years of life. The thick lines forming the reticulum were produced by narrow canals (clefts, or hyaline bars, as shown in figure 1 *D*) between which the tissue appeared to be crossed by fine furrows. Later, in the central area of the cornea a layer-like cloudiness appeared which was observed by oblique illumination. All other changes, such as the superficial glassy nodules with raised epithelium, were recognized only by retroillumination. Because the surface became irregular early in life, the visual acuity was early diminished. The sensibility was greatly diminished. There was no connection between the lattice-like fibers, or lines, and the corneal nerves.

ETIOLOGY AND PATHOGENESIS

A. Fuchs [17] regarded the disease as probably a primary and transmitted degeneration of connective tissue allied in nature to arteriosclerosis. Groenouw [2] in his 1917 report called the disturbance a hereditary predisposition affecting the corneal stroma itself or leading to a deposition of pathologic products in its layers.

One of the earlier conceptions, that of E. Fuchs,[15] was that impaired nutrition was responsible for the lesions. Support for this contention is the fact that the central area, where the metabolic processes are less active, is more affected than the periphery or may be the sole area affected. Endocrine insufficiency was first suggested by Wirth,[18] in 1926. Adrogué [19] in 1925 suggested that the disease developed as a result of herpes. Collins [16] regarded it as a neurotrophic disturbance of the nerve fibers and end organs. This view found favor with Kraupa,[20] Löwenstein [21] and others. Kraupa and Löwenstein's microscopic observation showed that the lesions, i. e., the nodular swellings and lattice-like opacities, were connected with the corneal nerves. On the other hand, Stanka,[22] working in the same clinic, by staining with 10 per cent solu-

17. Fuchs, A.: Zur Kenntnis der gittrigen Hornhautentartung (Haab-Dimmer), Ztschr. f. Augenh. **57**:159-186, 1925.

18. Wirth, M.: Zur Histologie der knötchenförmigen Hornhauttrübung, Ztschr. f. Augenh. **58**:106-114, 1926.

19. Adrogué, E.: Sobre la degeneración en malla o en reja de la córnea, Rev. Soc. argent. de oftal. **1**:32-39, 1925.

20. Kraupa, E.: Ueber einen Spaltenlampbefund an den Hornhautnerven bei einem Fall von degenerativer Hornhautveränderung, Klin. Monatsbl. f. Augenh. **68**:448-450, 1922; Zur Genese der gitterförmigen degenerativen Hornhautveränderung, ibid. **70**:179-180, 1923.

21. Löwenstein, A.: Erbliche Hornhautdegeneration, Klin. Monatsbl. f. Augenh. **32**:522, 1929; Zur Klinik, Histologie und Therapie der gitterförmigen Hornhautdegeneration, ibid. **82**:752-762, 1929.

22. Stanka, R.: Ueber familiäre gittrige Hornhautdegeneration, Klin. Monatsbl. f. Augenh. **74**:357-360, 1925.

tions of brilliant cresyl dyes demonstrated that the grill work was not connected with the corneal nerves. Wehrli [23] (1905-1909) stated the belief that the condition was an inactive form of tuberculosis, and Green,[24] in 1909, reporting improvement with therapy directed against tuberculosis, supported his view. Schieck [25] stated, however, that tuberculosis was probably an associated finding. Other possible causes have been mentioned by other authors.

The only conclusion one can draw at the present time is that the etiologic basis is obscure and belongs to some disturbance of the genetic factors in the chromosome makeup.

There has been a certain amount of controversy regarding the pathologic changes and the pathogenesis of the condition, which are certainly still obscure. Most of the authorities agree that it is a degenerative process. Chevallereau,[26] back in 1891, was the first to report on an anatomic examination of some affected tissues. He found rosette-like crystalline deposits of sodium urate in between the corneal fibers. On reviewing his work, E. Fuchs concluded that possibly the case was not a typical case of familial corneal dystrophy. Groenouw [27] studied histologically a small superficial piece of tissue excised from the cornea of one of his patients. He clearly observed that there was a foreign material deposited in the superficial laminae of the corneal stroma, sometimes reaching deep to the epithelium but not involving it. He noted that this substance gave an acidophilic reaction with hematoxylin and eosin and regarded it as of hyaline nature. In the vicinity of the hyaline patches he found the nuclei increased in number. The epithelium on the whole remained unchanged, and Bowman's membrane was mostly absent. He found no signs of any inflammatory process.

Wehrli [23] regarded the pathologic changes as a tuberculous process. He described at first flat sections of his excised tissue and noted that

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23. Wehrli: Die Knötchenförmige Hornhauttrübung (Groenouw) eine primäre, isolierte, chronische, tuberkulöse, Erkrankung der vorderen Schichten der Cornea —Lupus corneae, Ztschr. f. Augenh. **13**:322, 461 and 558, 1905; Weitere klinische und histologische Untersuchungen über den unter dem Bilde der knötchenförmigen Hornhauttrübungen (Groenouw) verlaufenden chronischen Lupus der Hornhaut, Arch. f. Augenh. **55**:126-184, 1906; Neue klinische und histologische Untersuchungen ueber die Aetiologie der knötchenförmigen Keratitis (Groenouw), Ber. ü. d. Versamml. d. ophth. Gesellsch. **34**:175 and 312, 1907; Ein neuer Fall von knötchenförmigen Keratitis, Klin. Monatsbl. f. Augenh. **47**:241, 1909.

24. Green, J.: Nodular Opacity of the Cornea, J. A. M. A. **53**:920-924 (Sept. 18) 1909.

25. Schieck, F.: Die familiäre Hornhautentartung, in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1931, vol. 4, pp. 298-403.

26. Chevallereau, A.: Kératite goutteuse, France méd. **38**:321, 1891; abstracted, Jahresb. ü. d. Leistung d. Ophth. **22**:257, 1891.

27. Groenouw: Knötchenförmige Hornhauttrübungen, Arch. f. Ophth. **46**:85-102, 1898.

there were nests of cells, which he regarded as tuberculous nodules. In his second work, he described a cross section through such a nodule from the same patient and added that, besides the cellular proliferation, there was present an accumulation of amorphous, finely granular material between the corneal lamellas, over which Bowman's membrane was largely destroyed. He was unable to come to any conclusion regarding the nature of the substance. Paderstein [28] found a hyaline substance situated in front of Bowman's membrane, partly homogeneous and partly in the form of superimposed layers, granules and clumps which raised the epithelium. The underlying Bowman membrane was largely defective; the corneal stroma, however, remained everywhere unchanged. Zentmayer [29] simply stated that the changes observed in the affected area were of hyaline nature. E. Fuchs [7] in 1902 stated that the opacities

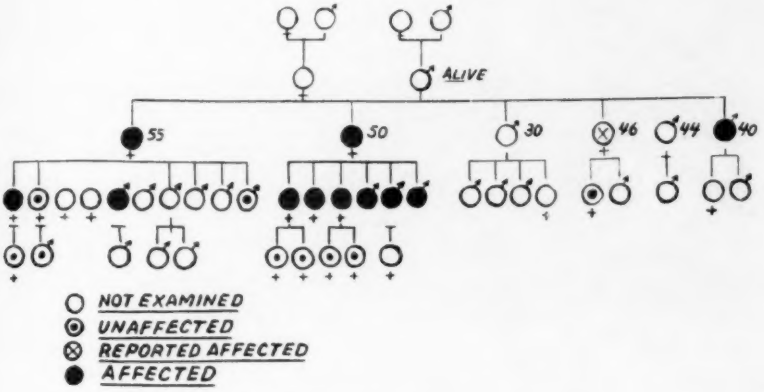

Fig. 2.—Genealogic tree of cases reported.

were an amorphous substance and in his [15] investigations in 1915 declared that they consisted of two different substances, namely a homogeneous and laminated acidophilic material and a granular basophilic substance. The deposition of the latter was probably primary, whereas the acidophilic substance was deposited only secondarily. He postulated that the acidophilic substance was probably derived from the basal cells of the epithelium, whereas the basophilic material had its origin in the tissue fluid present in the corneal stroma. He was unable

28. Paderstein: Zur Pathologie der Knötchenförmigen Hornhautdegeneration, Klin. Monatsbl. f. Augenh. **47**:156-165, 1909; Bermerkungen zu Wehrli's Kritik meines Falles von Knötchenförmigen Hornhautdegeneration, ibid. **47**:604-606 1909.

29. Zentmayer, W.: Nodular Opacities of the Cornea: Report of a Case, Ophthalmology **5**:628-633, 1909. Zentmayer, W., and Rush, C.: Nodular Degeneration of the Cornea, in Contributions to Ophthalmic Science Dedicated to Dr. Edward Jackson, Menasha, Wis., George Banta Publishing Company, 1926, pp. 115-121.

to draw any conclusions regarding the chemical nature of these two substances other than that they could not be regarded as either hyaline or colloid.

STUDY OF A PEDIGREE

In the genealogic tree presented (fig. 2), I have examined 15 adults and 6 children. Of the 15 adults, at least 11 show the disease. One other member (patient 14), not yet examined, is said by the family to have the disease. None of the 6 children examined presented the lesions. The oldest child is 9 years of age.

CASE 1.—Mrs. N. aged 50, of Italian extraction, had had no illnesses of note and was in perfect health. There had been no known consanguinity in the family. The patient stated that she had found difficulty in reading for the past few years. She did not recall any ocular trouble or injury. Her father was alive, but she did not know whether or not he had spots in his eyes. Her mother was dead, and nothing was known of her ocular condition. Her visual acuity was 20/100 in the right eye corrected to 20/30 and 20/100 in the left eye corrected to 20/40+2. Addition of a +2.00 D. sphere to each eye allowed Jaeger type 1 to be read with ease. Each cornea presented numerous gray-white opacities distributed entirely within the central area (fig. 3). They varied in size from minute spots seen only with the slit lamp to spots approximately 0.5 mm. in diameter; some of them were closely grouped. The right eye was more involved than the left. Slit lamp examination with oblique illumination revealed the larger spots to be composed of fine dotlike opacities grouped together. By retroillumination and scleral scatter they appeared like snowflakes. They were mainly situated immediately behind Bowman's membrane, some of them perhaps involving it. A smaller number were found in the deeper areas of the corneal stroma, extending backward about two thirds of the thickness of the cornea. The corneal surface was perfectly smooth and of normal luster. There was no loss of corneal sensibility. No linear formations were noted, nor was there any evidence of previous or present inflammation. The lens, vitreous and fundus appeared to be normal.

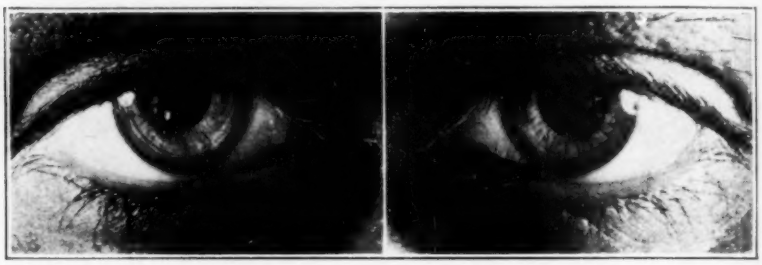

Fig. 3 (case 1).—Crumblike corneal opacities.

CASE 2.—L. N., aged 28, oldest son of Mrs. N. (patient 1), had no complaints and appeared to be in perfect health. His visual acuity was 20/20 in each eye. The corneas contained lesions similar to but less severe than those of his mother (fig. 4). In this case, too, there was no history or evidence of any type of irritation or inflammation. No sign of loss of corneal sensitivity was elicited. The lens, vitreous and fundus were normal.

CASE 3.—Mrs. A. R., aged 26, oldest daughter of Mrs. N., also had no complaints. Her visual acuity was 20/20 in the right eye and 20/20 + in the left. In the right eye seven to ten flat corneal spots with irregular borders were noted on focal illumination. These were central in position. In the left eye, in addition to the flat corneal opacities, there were two linear opacities about 6 mm. long bearing a large nodule at each end. Smaller nodules were noted on and alongside the streaks. There was no loss of corneal sensation. The lens, vitreous and fundus were normal. The patient had two children, one aged 6 years and the other 18 months. Neither of them showed any abnormality of the cornea by oblique illumination.

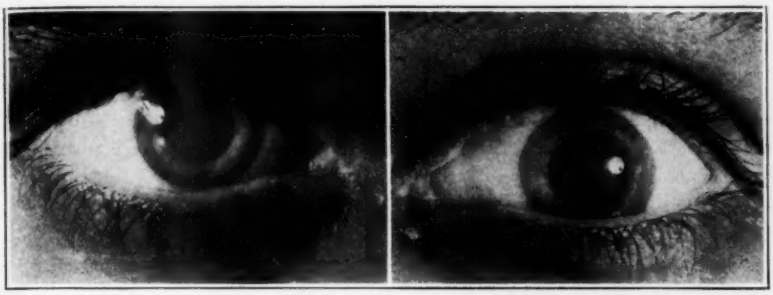

Fig. 4 (case 2).—Crumblike corneal opacities; unretouched photograph.

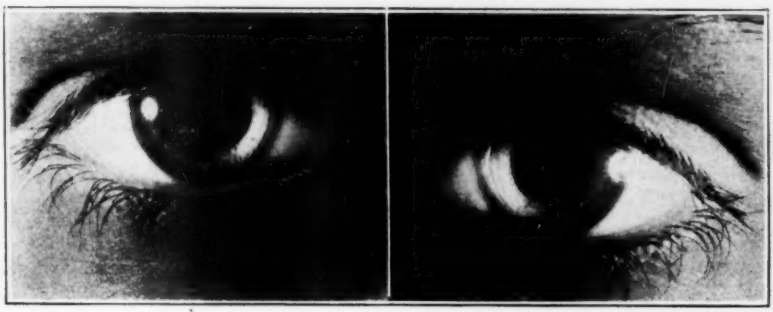

Fig. 5 (case 3).—Crumblike corneal opacities; unretouched photograph.

CASE 4.—J. N., aged 25, son of Mrs. N., had numerous irregular opacities, more prominent in the left eye than in the right. In his left eye, near the nasal side, one or two irregularly serrated streaks were observed. His vision in the right eye was 20/30 — 2, or 20/20 — 3 with a correction of — 0.75 D. cyl., axis 180, and in the left eye, 20/40 or 20/20 — 2 with a correction of — 1.75 D. cyl., axis 180. The ophthalmometer showed a perfectly smooth surface with an astigmatism of 1.25 D. cyl., axis 95 in the right eye and of 2.25 D. cyl., axis 95 in the left. There was no diminution of corneal sensibility. The lens, vitreous and fundus were normal. The patient was in good health and has been accepted for service in the Army.

CASE 5.—Mrs. P. R., aged 23, daughter of Mrs. N., showed no abnormalities on physical examination. A serologic test was negative for syphilis. The visual acuity was 20/20+4 in each eye. The cornea of each eye presented numerous

nodular opacities, some of the larger ones being connected both by fine and by stubby linear opacities in an irregular fashion (fig. 5). The corneal sensation and the lens, vitreous and fundus were all normal. Focal illumination of the cornea of the patient's 2 children, one aged 3 years and the other 6 months, revealed no abnormalities.

CASE 6.—Mrs. M. K., aged 20, daughter of Mrs. N., was in perfect health. Her visual acuity was 20/15 in each eye. The corneas showed mainly the linear type of opacity, mild in degree, with the right eye more involved than the left. Several smaller flat nodular opacities were also present, seen more clearly by slit lamp. The cornea was smooth and the sensibility normal. The lens, vitreous and fundus were normal.

CASE 7.—D. N., aged 19, youngest son of Mrs. N., was in perfect health. His visual acuity was 20/20+3 in both eyes. The left cornea was clear and showed nothing abnormal on slit lamp examination. The right eye presented a solitary faint grayish macula on the nasal side of the cornea. On slit lamp study it was found to be in the superficial layers of the parenchyma, its periphery touching the membrane of Bowman. No other spots were discovered. The corneal surface was smooth, and the sensibility was not diminished. The lens, vitreous and fundus were normal.

CASE 8.—Mrs. T. R., aged 56, a sister of Mrs. N., was an obese, hard-working housewife who claimed that she suffered from disease of the heart and of the gallbladder. She stated that in the past five or six years her vision had become poor but that she had never worn glasses. On examination by oblique illumination, numerous (thirty to forty) ring-shaped, irregular, oval and circular grayish white opacities were observed. The cornea was smooth and of normal luster and sensibility. The lens, vitreous and fundus were found to be normal.

CASE 9.—W. R., aged 32, son of Mrs. T. R. (patient 8), stated that he had been wearing glasses for five or six years. There was no history of irritation or inflammation. He had always been in good health. He showed corneal opacities bilaterally, more marked in the left eye. These appeared only as dots, seen with difficulty on oblique illumination without the loupe. With the aid of the loupe they were found to be ringlike in form.

CASE 10.—Rose, aged 27, daughter of Mrs. R., was in good health and with oblique illumination with the hand loupe showed no lesion. Her son, aged 9 months, was likewise found to be unaffected.

CASE 11.—N. R., aged 19, son of Mrs. R., was in good health. When examined with the hand loupe and oblique illumination, he also was found to be free of the disease.

CASE 12.—Mrs. A. B., aged 39, oldest daughter of Mrs. R., complained of poor vision without her glasses. Her general health was good, and she had no general complaints. Her visual acuity was not determined, for she was examined at her home. She was at the time wearing a moderately strong hypermetropic correction, which she said improved her vision very much. On examination of the corneas with oblique illumination and with the aid of the loupe—and with the + 20 lens of the ophthalmoscope—numerous irregular whitish gray spots were observed, involving the central area and leaving the periphery of the cornea for a width of 2 to 3 mm. free. The opacities were varied in form, being of the crumblike, as well as the stocky linear, type. No loss of sensation could be detected with cotton wool. The lens, vitreous and fundus were normal.

CASE 13.—M. B., aged 9, only daughter of Mrs. A. B. (patient 12), was in perfect health and gave no history of any visual complaints. Examination of her eyes with oblique illumination and the hand loupe revealed no corneal anomaly or abnormality. The lens, vitreous and fundus were normal. The visual acuity was not determined and slit lamp examination was not performed, since the daughter as well as the mother was seen at home.

CASE 14.—Jennie, aged 46, sister of Mrs. N., was not examined but was said by her daughter to have "spots" on her eyes.

CASE 15.—Constance, aged 19, daughter of Jennie (patient 14) had corneas seen to be free from opacities on oblique illumination. The corneal sensibility was normal, as were the lens, vitreous and fundus.

CASE 16.—N. M., aged 44, brother of Mrs. N. (patient 1), had been in good health until recently, when he was taken suddenly ill with coronary thrombosis. This patient was first seen in November 1941. He presented left divergent concomitant strabismus. He gave a history of having had convergent strabismus when a young child. At the age of 14 he had been operated on for the first time, only to have this converted to a divergent type. Another operation was performed a year later, but without any improvement. The patient never returned for a third operation. He had had no other ocular trouble. He had been wearing glasses for the past twenty-nine years. His visual acuity was as follows: right eye, 20/200, or 20/22 with a correction of + 3.50 D. sph. ⊃ — 0.75 D. cyl., axis 25; left eye, counting of fingers at 2 feet (60 cm.), unimproved with a correction of + 5.00 D. sph. ⊃ — 1.25 D. cyl., axis 180. An addition of + 0.75 D. sph. for each eye allowed Jaeger type 1 to be read with ease. Examination of both corneas revealed no anomaly or abnormality. The media of the right eye were clear; the left eye presented some Morgagni globules in the lens and numerous floaters in the vitreous. Examination of the fundi revealed an early type of arteriosclerosis. The arteries showed an increased light reflex, the smaller vessels appeared attenuated and some of the larger vessels showed some irregularity in caliber. There were no hemorrhages or exudates, and the maculas and peripheries were essentially normal. The left eye was turned outward, and, in addition to having a limited internal rotation, presented two irregular masses of granulation tissue, one at each canthus, at the site of previous operations. The rotation of the right eye was good in all directions. Measurements with the Javal ophthalmometer revealed no irregularity of the surface, and an astigmatism of 2 D. cyl., axis 90 was found in each eye. No slit lamp examination was performed. A son, aged 7 +, was not seen.

CASE 17.—C. M., aged 40, a brother of patient 1, was in perfect health. He had had poor vision for many years and had never had an ocular examination. He had been wearing an old pair of glasses belonging to his brother, with some improvement in vision. Examination by oblique illumination revealed numerous irregular and crumblike grayish white opacities occupying the central area of the cornea and leaving the periphery free and clear. No further examination was performed, since the patient was seen at his place of business only. The son, aged 3+, was not examined.

SUMMARY AND COMMENT

Certain general features are evident from the cases here presented:

1. The condition is a hereditary disease showing mendelian dominance.

2. Consanguinity is not a factor.

3. It affects males and females equally.

4. It is bilateral.

5. It is more or less symmetric.

6. It is central in position.

7. The corneal surface is smooth.

8. Sensibility of the cornea is not diminished.

9. There is no history of irritation.

10. There is no evidence of inflammation.

11. The visual acuity is unaffected in the younger members and only slightly diminished in the older ones.

12. The reticular, nodular and ring-shaped varieties may coexist in members of the same family and even in the same person.

With reference to the last observation, that several morphologic forms of lesions are present, it may be stated that they all belong to one of the types of corneal dystrophy as classified by Bücklers.

Bücklers classified hereditary corneal dystrophy into the crumblike, the macular and the lattice-like. The features of the crumblike type are that the visual acuity and corneal sensibility may be only slightly diminished late in life and that it does not lead to blindness. The inheritance is dominant. Obviously, the disease in all the cases in the present series was of this type, Bücklers' type 1. The prognosis is good. In contrast, the other two types lead to blindness. The macular type of corneal dystrophy leads to early diminution of visual acuity with diffuse and rapid clouding of the cornea and early loss of sensibility. Inheritance of this type is recessive, and the lesion need not appear in every generation. Lastly, the lattice-like corneal dystrophy produces irregularity of the cornea early in life, with corresponding diminution of visual acuity and early loss of corneal sensibility. Inheritance is dominant.

As all the cases here reported have been under observation for a brief period, no comment can be made on the progressive tendency in this genealogic tree. I therefore refrain from taking a stand in the controversy regarding the pathogenesis and etiologic basis of this interesting familial condition.

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ROLE OF ASCORBIC ACID (VITAMIN C) IN SECRETION OF INTRAOCULAR FLUID

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OUTLINE

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I. INTRODUCTION

In a previous paper [1] certain components of the secretory mechanism in the ciliary body were described and a theory was formulated to explain

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1. Friedenwald, J. S., and Stiehler, R. D.: Circulation of Aqueous: Mechanism of Secretion of Intraocular Fluid, Arch. Ophth. **20**:761 (Nov.) 1938.

their interaction. The present study is a continuation of the same investigation. Ascorbic acid (vitamin C) is a substance derived from the blood but present in the intraocular fluid in a concentration appreciably higher than in the blood.[2] Energy must be expended by the tissues to maintain the difference in concentration. The previous study had revealed that energy was available in the ciliary processes for secretory work. We were interested, therefore, in inquiring whether the conceptions of the secretory mechanism previously formulated were adequate to explain also the intraocular secretion of ascorbic acid. The answer to this question constituted the initial objective of the present study. It was soon found, however, not merely that ascorbic acid is passively acted on by the secretory mechanism but that, in fact, the ascorbic acid system constitutes an integral part of the secretory mechanism. An adequate explanation of the mechanism of the intraocular secretion of ascorbic acid has not yet been achieved, but it has been found that one necessary component of the ascorbic acid–secreting mechanism is a simple corollary of the role of this substance in the energy transformation of fluid secretion.

In the previous paper it was shown that the energy of secretion could be derived from a difference in oxidation-reduction potential between the epithelium and the stroma of the ciliary body. This difference in potential was found to be the result of a difference in the respiratory enzymes of the two tissues.[3] The interaction of these two tissues through the intermediation of a barrier, or membrane, that existed between them could result in the transformation of the available energy into work. The barrier was shown to possess the characteristics of reversible oxidizability requisite for the function of mediation between epithelium and stroma. If a chain of redox reactions took place whereby the epithelium was continuously being reduced by the stroma, there would be a transfer of electrons from stroma to epithelium. This would have to be balanced by an ionic transfer. The passage of an ionic train through a charged membrane is associated with the transfer of water, i. e. electro-osmosis. The barrier between stroma and epithelium was found to possess a charge of the proper sign so that with the ionic current in the postulated direction water would be transferred toward the intraocular cavity.

In this theory of secretion the stroma of the ciliary body has been considered as a functional unit, and, in fact, the study of its oxidation-reduction potential revealed no differences between its component parts,

2. Müller, H. K., and Buschke, W.: Arch. f. Augenh. **108**:368, 1934.

3. Friedenwald, J. S., and Herrmann, H.: Bull. Johns Hopkins Hosp. **70**:1, 1942.

capillary endothelium, stroma cells and extracellular matter, the last-mentioned accounting for by far the largest portion of the tissue. But the oxidation-reduction potential is plainly derived from the action of respiratory enzymes on their metabolic substrates. It follows that the well stabilized potential and the large reducing capacity which were found to characterize the interstitial tissue of the ciliary stroma must be due to the presence in the extracellular fluid either of respiratory enzymes and metabolites or of some reversibly oxidizable substance or substances which can diffuse into and out of the cells and hence maintain in the extracellular spaces the potentials generated within the cells. Preliminary tests showed that protein-free extracts of the ciliary body contained considerable amounts of reversibly oxidizable substances. We set ourselves the task (*a*) of identifying these redox substances and (*b*) of determining their normal location in the tissue.

The continuity of the argument will be maintained in the large type of the text. Experimental technic and experimental protocols are given in small type. A brief summary is given at the end of each section.

II. REDOX SUBSTANCES IN THE CILIARY BODY

A. TITRATION AND IDENTIFICATION

Protein-free extracts of ciliary body and of other tissues for comparison were examined for redox material by titration with potassium iodate, methylene blue and 2,6-dichlorophenolindophenol. Potentiometric titration curves for the identification of ascorbic acid were determined. Glutathione was estimated by the glyoxalase reaction.

1. Technic.—Extracts: Tissues taken as fresh as possible from animal eyes were promptly frozen in precooled and weighed centrifuge tubes. After they were ground in the frozen state, their weight was determined. About three times this weight of 4 to 8 per cent sulfosalicylic acid was added and the tissue extracted with vigorous rubbing for several minutes, after which the extract was separated by centrifuging. Alternately, 8 per cent trichloroacetic acid was used for extraction, and if large amounts of tissue were available, the grinding was done with sand in a mortar.

The iodometric titration was done with potassium iodate (KIO_3)[4] in the presence of 0.1 cc. of 1 per cent potassium iodide (KI) per 0.2 to 0.5 cc. of acid extract.

The methylene blue titration[5] was done at a p_H of about 4.9 (acetate buffer) in the presence of 0.1 cc. of saturated sodium thiosulfate per 0.5 cc. of original acid extract. The illuminating system used for activation of the reaction was cooled by a stream of air. As a further precaution against reoxidation of the leuko-

4. Woodward, G. E., and Fry, E. G.: J. Biol. Chem. **97**:465, 1932. Wachholder, K.: Ztschr. f. physiol. Chem. **233**:181, 1933.

5. Martini, E., and Bonsignore, A.: Biochem. Ztschr. **273**:170, 1934. Neuweiler, W.: Klin. Wchnschr. **15**:854, 1936. Lund, H., and Lieck, H.: Klin. Wchnschr. **16**:555, 1937.

methylene blue by air during titration, the diameter of the titration vessels and hence the surface of contact of the fluid with air was kept small (1 to 2 cm). The procedure was standardized (in respect to p_H effect) by adding a known amount of ascorbic acid to a second sample of the buffered and thiosulfate-containing extract and determining its titration value.

2,6-dichlorophenolindophenol [6] (sodium 2,6-dichlorobenzenoneindophenol) titration in acid solution requires no special comment. For titration of small volumes the acid extract is taken up in a fine glass capillary. One to three drops is expelled into a minute test tube (internal dimensions, 3 by 20 mm.). A glass bead is introduced to facilitate mixing, which is accomplished by tapping the tube with a finger nail. From a similar capillary successive drops of 0.003 normal solution of the dye are added until a permanent color is obtained. The drop sizes of the capillaries are calibrated by titrating a standard solution of ascorbic acid with them. With care the method may be made sensitive to 0.5 microgram of ascorbic acid.

Potentiometric Titration: Ball [7] has shown that solutions of ascorbic acid and dehydroascorbic acid in definite proportions at definite p_H exhibit characteristic potentials, which may be measured with appropriate electrodes, etc. It follows that if under nitrogen and at a fixed low p_H small amounts of an oxidant (ferricyanide) are added successively to a solution containing ascorbic acid and the potential measured after successive additions, a relation may be established between the potential recorded and the percentage of ascorbic acid oxidized, which is highly characteristic for this substance. Ball has used this potentiometric titration to identify the redox material in orange juice as ascorbic acid. The method has, however, not heretofore been used for micro estimation or for identification of ascorbic acid in the presence of other reducing substances.

By use of a suitable small titration chamber (a cylindric vial 12 mm. in diameter and 30 mm. high), titration may be performed on as little as 0.5 cc. of acid extract of tissue. The upper end of the titration chamber is closed by a rubber stopper through which five glass tubes are admitted, each approximately 2 mm. in diameter. These include a freshly gold-plated platinum electrode, a potassium chloride-agar bridge to a calomel (mercurous chloride) half-cell, the outlet of a microburet through which measured amounts of an oxygen-free solution of ferricyanide may be delivered, an inlet for oxygen-free nitrogen saturated with water vapor and an outlet for the nitrogen.[8] Test runs with known solutions of ascorbic acid of 0.01 to 0.001 molar concentration with this apparatus reproduced Ball's curves exactly. At p_H 4 to 5 the electrodes reached equilibrium with the solutions somewhat sluggishly, requiring five to thirty minutes. When concentrations of ascorbic acid of 0.0001 molar were used, the sluggishness of the electrodes was greatly increased, equilibrium being reached only after many hours, and an end point of negative drift of the potential of 0.1 millivolt per minute was selected somewhat arbitrarily for the reading. At low p_H the sluggishness of the reaction was further increased, while at p_H above 5 the spontaneous decomposition of the dehydroascorbic acid prevented the establishment of equilibrium. Consequently, our titrations were performed at p_H 4.62 (acetate buffer). An added mediator, e. g., methylene blue or Lauth's violet, or traces of iron or copper did not enhance the rate of reaction when ferricyanide was used as the oxidant, and

6. Birch, T. W.; Harris, L. J., and Ray, S. N.: Biochem. J. **27**:590, 1933.

7. Ball, E. G.: J. Biol. Chem. **118**:219, 1937.

8. Clark, W. M.: Determination of Hydrogen Ions, ed. 3, Baltimore, Williams & Wilkins Company, 1928, p. 300.

with this alone the best results were obtained, an initial dose of 0.001 molar potassium ferrocyanide being introduced into the chamber at the beginning of the titration. Under these conditions and with intervals of two to six hours allowed after each addition of oxidant for the establishment of equilibrium, the theoretic titration curve could be reproduced with 0.5 cc. of 0.0001 molar solution of ascorbic acid with a deviation of less than 5 millivolts.

The use of this technic on a protein-free tissue extract containing several different redox substances can be expected to yield a titration curve one portion of which will reproduce the characteristic ascorbic acid titration curve only if those substances which are present in addition to ascorbic acid do not form complexes with ascorbic acid or its oxidation product, do not react with them except in redox fashion and do not themselves yield normal potentials close to that of the ascorbic acid system. Hence, this method is not necessarily of general applicability, and it is not to be assumed that the cleancut results we obtained with extracts of ciliary body and of some other tissues will be repeated with all other organs which contain large amounts of ascorbic acid.

Glyoxalase: Schroeder and Woodward's[9] method of estimating glutathione was used without modification.

2. *Results.*—Protein-free extracts of the ciliary body gave a pink color with sodium nitroprusside. The color was not obtained with extracts previously treated with monoiodoacetic acid. Consequently we concluded that a sulfhydryl compound was present and tested for glutathione by the glyoxalase reaction. The results showed that glutathione was present in the tissue in concentrations of approximately 2 milliequivalents (per thousand grams of fresh tissue). It was of interest to discover whether any considerable portion of the glutathione existed in the tissue in the oxidized state. A sample of tissue extract was divided into two portions, one of which was treated with hydrogen sulfide, which was afterward removed by bubbling nitrogen through the solution. The two portions were then tested with glyoxalase and produced approximately equal activity. Supposing that oxidized glutathione might be less readily extractable from the tissue than reduced glutathione, we removed the iris and ciliary body simultaneously from the two eyes of a rabbit. One specimen was frozen and extracted in the usual manner. The second specimen was placed in an atmosphere of nitrogen for fifteen minutes before acid was added for extraction. The two extracts when titrated with glyoxalase showed equal amounts of glutathione within the limit of accuracy (5 to 10 per cent) of the method. It is concluded that not more than 5 to 10 per cent of the glutathione in the tissue is normally in the oxidized state.

Comparing the results of glyoxalase titration with those of iodine, methylene blue or indophenol titration (table 1) on the same sample, we found that glutathione represents approximately 40 to 50 per cent of the total (iodine-titratable) redox material in the extract and is equal to the difference between the iodine-titratable material and that titratable

9. Woodward, G. E.: J. Biol. Chem. **109**:1, 1935.

by the methylene blue or the indophenol procedure. The tests were made on the isolated ciliary processes of cows' eyes and on the combined ciliary body and iris of rabbits and pigs. Essentially similar results (table 1) were obtained with all three species, though the figures for methylene blue and indophenol were somewhat lower for pigs.[10]

That portion of the redox material which is titratable with methylene blue and with indophenol might be ascorbic acid. Nevertheless, the specificity of the two tests leaves much to be desired. The most specific test for ascorbic acid is the prevention of scurvy in guinea pigs, and at least part of the reducing substance in the aqueous of cows' eyes has been shown to be ascorbic acid by this means.[11] In spite of the high concentration of reducing substance in the ciliary body, the volume of the tissue is so small that approximately 1,000 rabbit ciliary bodies would have to be extracted to provide sufficient material for one complete feeding test. Furthermore, any estimate of quantity on the basis of such a biologic assay is associated with a wide margin of uncertainty.

Potentiometric redox titration as described serves as a highly specific method of identifying ascorbic acid. With concentrations of ascorbic acid similar to those anticipated in the tissue extracts, the theoretic titration curve of ascorbic acid was reproduced with an accuracy of $\pm$ 0.005 volt. Similar titration on known solutions of glutathione gave less reproducible results. The shape of the glutathione titration curve and its position in the scale of potential was influenced by the absolute concentration of glutathione, the duration of the titration, the state of the electrodes and other undisclosed factors. This was to be expected in view of the known anomalies of behavior of this substance on electrometric titration.[12] In general, with concentrations expected in the tissue extracts, the midpoint of the titration curve for glutathione was found approximately 0.1 volt more negative than that of ascorbic acid at the same p_H.

Titration of protein-free tissue extracts yielded curves one portion of which could be superimposed on the theoretic titration curve of ascorbic acid as established by Ball. An uncertainty of $\pm$ 0.005 volt in the position of the midpoint of the titration curve yields an uncertainty of $\pm$ 15 per cent in the estimate of the total ascorbic acid present (fig. 1).

The amount of ascorbic acid computed from the titration curve plus the amount of glutathione as established by the glyoxalase titration accounted for the total ferricyanide used in the titration within the

10. Tissue could not be obtained as fresh from pigs as from cows or as fresh from cows as from rabbits and other laboratory animals.

11. Demole, V., and Müller, H. K.: Biochem. Ztschr. **281**:806, 1935.

12. Michaelis, L., and Flexner, L. B.: J. Biol. Chem., **79**:689, 1928.

expected errors (10 to 15 per cent) of the methods. The total iodine and the ferricyanide titration were in close agreement. The results of these experiments indicate that ascorbic acid plus glutathione account for substantially all the redox material present. The experiments show that for the tissues studied the indophenol and the methylene blue titration give a reliable measure of the ascorbic acid present.

One further point of interest may be mentioned. If pure ascorbic acid and glutathione are mixed in a buffer solution and titrated in the manner described, a curve is obtained no portion of which fits the theoretic curve for ascorbic acid. This result was to have been expected, since it is well known that at the p_H of the titration (p_H 4.62) the reaction

dehydroascorbic acid + 2 G S H → ascorbic acid + G S S G

proceeds extremely slowly or not at all. In fact, it is the sluggishness

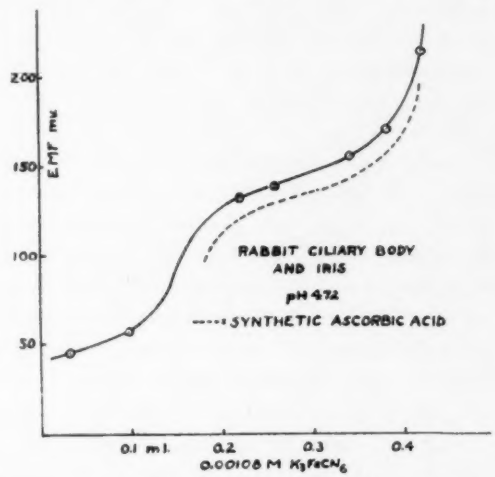

Fig. 1.—Potentiometric titration curve of protein-free tissue extract compared with that of synthetic ascorbic acid. The electromotive force (*E M F*) is recorded in millivolts, zero E M F being that of a calomel half cell.

of this reaction at low p_H which enables one to titrate ascorbic acid with indophenol or methylene blue in the presence of glutathione. The titration on tissue extracts indicates that the reaction proceeds more rapidly and more completely in the extract than in the pure solution. Apparently the extract contains some substance which catalyzes the reaction.

Summary.—Protein-free extracts of the ciliary processes of cows and of the ciliary body and iris of rabbits and pigs contain approximately 4 milliequivalents of reducing substances, of which 50 to 60 per cent may be identified as ascorbic acid and the remainder as glutathione, together with possible traces (not more than 15 per cent) of unknown substances.

B. LOCATION OF THE REDOX SUBSTANCES IN THE TISSUE

1. *Ascorbic Acid.*—Having identified the major portion of the redox substances present, we had the task of discovering if possible the position normally occupied by these substances in the tissues. Szent-Györgyi,[13] in his studies on the reducing substances in the adrenal gland, studies which culminated in the isolation and identification of ascorbic acid, developed histologic technics for the demonstration and localization of reducing substances in the tissues. These technics have been modified and their specificity in respect to ascorbic acid increased through control of p_H by Giroud and LeBlond.[14] We have applied them to the ocular tissues, the tests being performed at p_H 4.

In the technic used, metallic silver is deposited in the form of black granules in the tissue wherever substances capable of reducing silver nitrate exist in adequate concentration. On microscopic examination black granules are found in the stroma of the ciliary processes. The granules are not accumulated within the endothelial cells of the capillary walls, though some are present on the cell surfaces. The granules are fairly uniformly distributed in the extravascular tissue of the stroma of the ciliary processes—equally within the stroma cells and in the interstitial tissue. Only a few granules are found in the epithelium, mainly on the cell surfaces. Similarly, few granules are found in the ciliary muscle. Some granules are present in the iris; these are most concentrated near the anterior surface. Glutathione does not reduce silver and hence can play no part in the reaction. Previous studies have shown that the tissue dehydrogenases are inactive at p_H 4, and in any case the tissue enzymes must be precipitated and inactivated by the silver nitrate. Hence the reduction of the silver must be attributed to the ascorbic acid which is present, not to normally inactive metabolites activated by enzymes. These experiments do not prove the absence of ascorbic acid in the epithelium—a point to which we shall return later—but they do prove the presence of ascorbic acid in the extravascular and interstitial tissue of the ciliary stroma. In fresh ciliary processes approximately one third of the wet weight is epithelium and one third blood. If all the ascorbic acid found is in the stroma, the concentration there is of the order of 0.003 molar.

If a solution of ascorbic acid in higher concentration than that normally present in the aqueous is injected into the anterior chamber, the intensity of the silver stain in the iris becomes pronouncedly increased and that in the ciliary processes only slightly so. If a large dose (0.5

13. Szent-Györgyi, A.: Biochem. J. **22**:1387, 1928.

14. Giroud, A., and LeBlond, C. P.: L'acide ascorbique dans les tissus et sa détection, Paris, Hermann & Cie, 1936.

Gm.) is injected intravenously into a rabbit, the intensity of the stain in the ciliary processes is markedly increased.

2. *Glutathione.*—The use of the sodium nitroprusside reaction to determine the position of the glutathione in the tissue resulted in a color which in most instances was too feeble for microscopic localization. In a few instances, however, the fact that part of the reaction occurred in the stroma could be established.

3. *Summary.*—A portion of the ascorbic acid and probably also of the glutathione present in the ciliary stroma is normally located in the extracellular interstitial fluid of that tissue and is, therefore, capable of accounting for the well stabilized oxidation-reduction potentials previously found in that tissue. This redox system is likewise available to act as a mediator between the stroma cells and the stroma-epithelium barrier in the redox chain which we have previously postulated as a possible source of the energy of fluid secretion.

III. ASCORBIC ACID IN THE MECHANISM OF SECRETION OF INTRAOCULAR FLUID

In the previous section it was shown how the theory of the secretory mechanism led us to seek redox substances in the interstitial tissue of the stroma of the ciliary processes and how the presence of ascorbic acid in this location was established. We may now inquire whether the ascorbic acid actually plays a role in the secretory mechanism. In order to do so we have sought to discover what changes, if any, take place in the intraocular secretory mechanism on deprivation of vitamin C. Since rabbits are not susceptible to scurvy, it became necessary to extend our investigations to guinea pigs.

A. REDOX SUBSTANCES IN THE OCULAR TISSUES OF GUINEA PIGS

As a step preliminary to the study of the effect of vitamin C deprivation on the secretory mechanism, it was necessary to study the effect of diet on the ascorbic acid content of the ciliary body and of the aqueous in guinea pigs.

In estimating the redox material in the iris and in the ciliary body of guinea pigs, it was found necessary to pool the tissues of 10 to 18 eyes. Extraction and titration were performed as outlined previously. An estimate of the concentration of reducing substance in the aqueous can be made on the fluid (20 to 50 cu. mm.) obtained from a single guinea pig eye, micro titration with 2,6-dichlorophenol-indophenol, as described, being used.

It was found (table 1) that well nourished adult animals which have been fed a diet containing abundant vitamin C have reducing substance in the aqueous titratable with indophenol amounting to between 1 and 3 milliequivalents. These animals likewise have (iodine) reducing sub-

stance in the ciliary body and iris in a concentration of 3 to 4 milliequivalents. Of this, approximately 30 to 40 per cent is titratable with 2,6-dichlorophenolindophenol and can be shown to be ascorbic acid by electrometric titration. When these animals are placed on a vitamin C–free diet (dry oats, water and cod liver oil), the reducing substance in the aqueous rapidly decreases, reaching immeasurably small concentrations in four to six days. The disappearance of titratable reducing substance from the aqueous is accompanied by a decided decrease in the indophenol-titratable fraction of the ciliary body–iris extract. It is of particular interest that the decrease of ascorbic acid in the ocular tissues takes place before any visible constitutional symptoms of scurvy develop.

TABLE 1.—*Titrations of Reducing Substances in the Ciliary Body* *

	Chemical Titration			Electrometric Titration with Ferricyanide		
	Methylene Blue	2,6-Dichlorophenol-indophenol	Potassium Iodate	Estimated as Ascorbic Acid	Total Titration	Glyoxalase Test
Rabbit †.....	2.3 (3)‡	2.7 (3)	4.0 (2)	2.0 (3)	4.0 (3)	.....
Pig †.....	0.6 (2)	.....	2.7 (2)	.....	.....	.....
Cow §.....	1.9 (2)	2.1 (2)	3.7 (3)	2.0 (2)	3.0 (2)	.....
		2.5 (2)	4.3 (2)	.....	.....	1.6 (2)
Guinea pig †						
Vitamin C saturated....	.....	1.6 (2)	4.5 (2)	1.0 (1)	3.3 (1)	.....
Vitamin C deficient.....	.....	0.5 (1)	3.4 (1)	0.7 (1)	.....	.....
Cat ‖.....	1.5 (1)	2.2 (1)	.....	1.9 (1)	3.6 (1)	.....

* The values are given in milliequivalents per thousand grams of fresh tissue (1 milliequivalent of ascorbic acid equals 88 mg.; 1 milliequivalent of glutathione equals 137 mg.).
† Ciliary body plus iris.
‡ The figures in parentheses indicate the number of experiments.
§ Isolated ciliary processes.
‖ Ciliary body without iris.

When similar studies are made on young guinea pigs weighing approximately 200 Gm., it is found that the disappearance of ascorbic acid from the ocular tissues takes place even more rapidly. Twenty-four to forty-eight hours after the last vitamin C–containing meal, no titratable reducing substance is to be found in the aqueous. It is evident that these young animals are deficient in a capacity of storing ascorbic acid in their ocular tissues. Nevertheless, they do not show clinical symptoms of scurvy until they have been on the deficient diet for ten to fourteen days, and death occurs in three to four weeks. The lability of the ascorbic acid content in guinea pig eyes explains the widely discordant reports of previous investigators as to the "normal" concentration of ascorbic acid in the aqueous of guinea pigs. In order regularly to obtain animals with a high ascorbic acid content of the ocular tissues, special precautions must be taken to insure a high intake of vitamin C during the days and also the hours preceding an experimental observation.

In both adult and young animals that have been deprived of vitamin C, the intravenous injection of ascorbic acid is promptly followed by the reappearance of reducing substance in the aqueous. The silver staining which gives a negative result in the ciliary body of scorbutic guinea pigs gives a positive result promptly after the intravenous injection of ascorbic acid.

In summary, these experiments show that ascorbic acid is a normal component of the ocular tissues in the guinea pig as in the rabbit and, further, that ascorbic acid can be largely eliminated from the ocular tissues of guinea pigs by simple dietary restrictions without simultaneous production of such severe general malnutrition as to complicate the experimental picture. The extremely rapid depletion of the ascorbic acid reserve in the ocular tissues was an unexpectedly favorable circumstance greatly facilitating the further course of our study. Finally, these results show that 2,6-dichlorophenolindophenol titration of the aqueous furnishes a satisfactory index of the state of depletion of the ocular tissues.

B. OXIDATION-REDUCTION POTENTIAL

In the rabbit we have found a difference in oxidation-reduction potential between epithelium and stroma in the ciliary body and have assumed a possible interaction between these two tissues as the source of the energy of secretion. If the ascorbic acid system constitutes a link in the redox chain connecting the oxidases of the epithelium with the dehydrogenases of the stroma, then the withdrawal of ascorbic acid should inactivate the secretory mechanism. The inactivation would be manifest, among other things, in a change in the redox potential of epithelium and stroma. In the previous study on rabbits, redox dyes were used as indicators to determine the apparent potential of the ciliary tissues. With minor modifications we have applied to guinea pigs the technic reported in the previous paper. In general, aqueous was removed from one eye for indophenol titration, while the other eye was used for measurements of the oxidation-reduction potential. When it was desired to use both eyes of the same animal for measurements of the potential, e. g. before and after intravenous injection of ascorbic acid, a cage mate of similar size and age was used for titration control.

We are well aware that the use of indicators to determine redox potentials in living tissues is subject to considerable inexactitude. The activities of the dyes in the presence of tissue proteins probably differ from those in the simple solutions in which their normal potentials were standardized. In our previous paper, we reported briefly on the use of indicator dyes to determine the p_H of the tissue. Under appropriate conditions it was possible to show that the dye had approximately the same color in the tissue as in the surrounding buffer fluid. It follows that

the changes in activity of indicators in these tissues are not likely to introduce large errors, and this conclusion is fortified by the fact that consistent results are obtained with indicators of widely differing chemical characteristics. It will be pointed out hereafter that certain dyes are bound by the tissues, the binding naturally resulting in large displacements of their equilibrium constants, but such binding of the dyes involves the displacement of previously bound tissue components and proceeds slowly. Thus the binding of a dye can be recognized only when the tissue is exposed to the dye for a prolonged period (half an hour or more), while determination of redox potential is made as soon as a recognizable concentration of the dye appears in the tissue. In view of these well recognized errors of the indicator technic, it seems appropriate to refer to the results of our measurements as indicating "apparent redox potentials," and we desire that this reservation be understood throughout our discussion.

With this reservation, the meaning of the apparent redox potentials determined under conditions of equilibrium, i. e. under nitrogen asphyxia, should be clear. The application of similar measurements to actively respiring tissues is apparently less readily understood.[15] Within the respiring cell there is a continuous cascade of linked oxidative reactions. In meaning, an "apparent redox potential" determined in this steady state of nonequilibrium is obviously different from one determined at thermodynamic equilibrium. But in this continuous stream of reactions, the indicator reaches a state of partial oxidation and reduction dependent on the rate of production in the cell of substances capable of oxidizing and reducing the indicator. Thus the apparent redox potential of respiring tissue has a real significance related to the respiratory activity of the cell, and a change in the apparent redox potential means a change in the rate of production within the tissue of some substance or substances capable of oxidizing or reducing the indicator. Furthermore, a difference in the apparent redox potential of two tissues, unless it is due to a difference in the activity of the indicator, means that the tissue with the higher apparent redox potential can oxidize the tissue with the lower apparent redox potential if the two tissues are connected by an appropriate set of redox mediators.

In making preparations for supravital staining and observation, we found that the iris and ciliary body of the guinea pig could not readily be stripped out of the eye, as they could with the rabbit. Hence, after equatorial section of the eyeball and removal of the lens and the vitreous, the anterior segment—cornea, anterior portion of the sclera, iris and ciliary body—was cut up into four to six wedge-shaped slices and placed on glass slides with the intraocular surface up. The ciliary processes of the guinea pig are relatively short and thick and are not readily lapsed over the edge of such a preparation. It was found best, therefore,

15. Davson, H., and Quilliam, J. P.: J. Physiol. **98**:141, 1940.

when testing the epithelium with a dye, to place a minute drop of the dye on the moist posterior surface of the iris, whence it spread readily to the anterior tips of the ciliary processes. In this way fairly sharp preparations could be obtained. The eyes were removed with the animals under ether anesthesia.

An alternative method of preparing the tissue was as follows: After the eyeball was bisected at its equator, the anterior segment was pinned down on a cork, corneal surface down. The lens and the vitreous were gently removed. The iris and ciliary body were grasped at one point, cut radially and then gradually peeled out, adhesions to the sclera being cut with scissors. The thread of tissue so obtained could be cut into small segments, which could be mounted on slides. In this way preparations as fine as those previously obtained from rabbit tissue may be obtained. The procedure, however, is somewhat prolonged, and, while suitable for certain aspects of this study, was not regularly used in the determination of oxidation-reduction potentials.

The apparent oxidation-reduction potentials are estimated with the aid of a series of indicator dyes, the amount of reduction of the dye in the tissue being estimated by comparing the color before and after addition of an oxidant, such as potassium ferricyanide.

The results of these tests, presented in tables 2 and 5, show that the apparent potentials of the ciliary tissues in the normal guinea pig are closely similar to those found in rabbits. When ascorbic acid is depleted from the tissues, the aerobic potential of the epithelium becomes more strongly positive and that of the stroma more strongly negative. The increase in reducing potential of the stroma cannot be attributed to the addition of some new reducing system to the tissue, since the anaerobic potential is unchanged. When ascorbic acid is reintroduced into the system by intravenous injection, the potentials of the ciliary tissues immediately revert to the normal level. In the time required to make the injection, remove an eye and expose the tissue to the test dye—two or three minutes—the transformation is complete. The rapidity of the change would indicate that ascorbic acid itself is directly responsible for the change rather than some substance which might become available indirectly as the result of the intravenous injection of ascorbic acid.

The simultaneous rise in potential of the stroma and fall in potential of the epithelium are clear evidence that ascorbic acid facilitates the oxidation-reduction interaction between epithelium and stroma and hence that ascorbic acid acts as a mediator between these two tissues. It follows also that in the normal animal such interaction between the two tissues is actually taking place. This feature of the secretory system, which was postulated in the previous paper, is now supported by direct experimental evidence.

It will be noted in table 2 that under cyanide poisoning the potential of the stroma is higher when ascorbic acid is present. Since the increased rate of oxidation which the higher value denotes cannot be

TABLE 2.—*Reduction of Indicator Dyes in the Ciliary Body of Guinea Pigs (Ether Anesthesia)* *

Dye	E'_o at p_H 7.4 Volts	Vitamin C Saturated				Vitamin C Deficient				Scorbutic Animals Immediately After Administration of 50 Mg. of Ascorbic Acid			
		Aerobic		Cyanide	Nitrogen	Aerobic		Cyanide	Nitrogen	Aerobic		Cyanide	Nitrogen
		E	S	E and S	E and S	E	S	E and S	E and S	E	S	E and S	E and S
Bindschedler's green	+0.211	++++	++++	++++	++++	++++	++++	++++	++++	++++	.....	.....	.....
2,6-dichlorophenolindophenol	+0.189	++++	++++	++++	++++	+++	++++	++++	++++	.....	.....	.....	.....
Toluylene diaminoindophenol	+0.115	+++	++++	++++	++++	0	++++	++++	++++	+++	.....	.....	.....
Toluylene blue	+0.101	++	++++	++++	++++	0	++++	++++	++++	++	.....	.....	.....
Lauth's violet	+0.050	0	++++	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
Methylene blue	−0.002	0	++++	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
Indigo trisulfonate	−0.099	0	++++	++++	++++	0	++++	++++	++++	.....	++++	.....	.....
Indigo disulfonate	−0.143	.....	+++	++++	++++	0	++++	++++	++++	.....	+++	++++	.....
Indigo monosulfonate	−0.175	.....	0	+++	++++	0	++++	++++	++++	.....	0	+++	.....
Phenosafranine	−0.269	.....	0	0	++++	0	++	+++	+++	.....	0	0	.....
Safranine, bluish	−0.270	.....	0	0	++++	0	+	++	++	.....	0	0	++++
Neutral red	−0.340	.....	.....	.....	0	0	0	0	0	.....	.....	.....	0

* 0 indicates no reduction; +, one third reduced; ++, one half to two thirds reduced; +++, two thirds to nine tenths reduced; ++++, over nine tenths reduced. S indicates stroma, and E, epithelium, as in the following tables.

attributed to oxidation arising in the epithelium, for the two tissues now have equal potential, it follows that in the tissues ascorbic acid reacts more rapidly with atmospheric oxygen than do the other cyanide-insensitive reducing substances, which remain even when ascorbic acid is absent. The nature of the catalyst responsible for the aerobic oxidation of ascorbic acid in the tissues is not revealed by these experiments, but its activity in the presence of cyanide suggests that it is not a heavy metal. In fact, the auto-oxidation of ascorbic acid in the tissues may be an artefact resulting from cyanide poisoning. The small difference between aerobic and anaerobic potential in the stroma in the absence of ascorbic acid indicates that the respiration of the stroma is limited essentially to the portion mediated by the ascorbic acid system.[16] The still smaller difference in potential between cyanide and nitrogen asphyxia in the vitamin C–deficient animal may be due entirely to the reaction of the test indicator (safranine) with atmospheric oxygen. The oxidation which goes on normally in the ciliary stroma when ascorbic acid is present can thus be completely accounted for by the oxidative contribution of the epithelium, plus possibly the aerobic oxidation of ascorbic acid. On the other hand, the fact that in the deficient animal the introduction of cyanide causes a slight decrease in potential indicates that some oxidation of the stroma by the cyanide-sensitive oxidase occurs even in ascorbic acid deficiency. The question arises, therefore, whether the stroma contains small amounts of such oxidase or whether, even in vitamin C–deficient animals, some small amount of interaction between stroma and epithelium may continue, mediated by some other less efficient component of the reducing substances or by traces of ascorbic acid remaining.

In the previous paper the use of the usual indophenol reagent (paraphenylenediamine and alphanaphthol) in demonstrating the presence of an oxidase in the epithelium was reported. With this reagent no evidence was found for the existence of this enzyme in the stroma, and it was concluded that the stroma lacked indophenol oxidase. It is possible, however, that at a strongly negative potential the reaction might be negative even though the enzyme was present in small amount. In order to test this possibility the following experiment was performed:

A sample of iris and ciliary body freshly removed from a rabbit was placed in Ringer's solution with 0.001 normal ferricyanide solution. After five minutes the yellow color of the ferricyanide could be observed in the stroma. The tissue was washed in Ringer's solution until this color had been removed and was then placed in the indophenol reagent. The characteristic color of indophenol blue

16. Capillary endothelium constitutes a considerable portion of the cellular elements of the stroma. If the capillary endothelium in other tissues is likewise dependent on ascorbic acid for its respiration, the implication of our findings in respect to the symptomatology of scurvy is obvious.

appeared promptly in the epithelium, indicating that the treatment had not inhibited the oxidase. Nevertheless, no color developed in the stroma beyond that faint blue which appeared also in the bathing fluid. This experiment was repeated on normal and on vitamin C–deficient guinea pigs, with similar results.

This experiment indicates that the stroma contains no indophenol oxidase and hence that the small cyanide effect on the stroma of C–deficient animals is to be attributed to a small residual interaction between stroma and epithelium.

One further feature of the measurement of potential requires comment. In the rabbit and in the guinea pig with ample ascorbic acid, the potentials of the tissues were found to be stable, remaining unchanged in tissue fragments in Ringer's solution for one-half to one hour. With the C–deficient guinea pig the strong reducing potential of the stroma begins to disappear shortly after the tissue has been removed from the body. In fresh tissue the reduction of several of the safranine dyes was readily demonstrated. A similar piece of tissue after being in Ringer's solution for fifteen minutes may be unable to reduce methylene blue.

A possible explanation of this phenomenon may be that if the ionic electric current was absent from the tissues, or very feeble, anions would more readily escape from the ciliary stroma. It is not unlikely that necessary metabolites and mediators might be lost from the stroma in this way.

In summary, the apparent oxidation-reduction potential of the ciliary tissues is profoundly affected by the presence or absence of ascorbic acid. In the absence of ascorbic acid, the stroma lacks a hydrogen acceptor for its dehydrogenase activity. In the presence of ascorbic acid, oxidation of the stroma by molecular oxygen takes place. A fraction of this oxidation may be attributable to aerobic oxidation of ascorbic acid and the major portion to the effect of enzymes which are capable of being inactivated by cyanide. These enzymes are present only in the epithelium. It is concluded, therefore, that oxidative-reductive interaction between epithelium and stroma takes place and that ascorbic acid acts as a mediator which facilitates this interaction.

C. IRRECIPROCAL PERMEABILITY TO DYES

In the previous paper it was pointed out that if oxidative-reductive interaction should take place between epithelium and stroma, an electric current would be generated which would manifest itself in the movement of ions, cations being transferred from stroma to epithelium and anions being transferred from epithelium to stroma. By introducing colored ions, i. e. dyes, into the tissue, this ionic migration may be made observable. We shall now discuss this technic applied in the presence and in the absence of ascorbic acid.

In the experiments of this type reported in the previous paper, the most striking illustration of ionic transfer was observed in the case of basic dyes. A sublethal dose of crystal violet is injected intravenously into a rabbit. Immediately after the injection is completed, one eye is enucleated, with the animal under ether anesthesia, and a portion of the ciliary body is placed on a slide for microscopic examination. It is found that almost all the dye in the ciliary body is already concentrated in the epithelium. The whole procedure can be performed in less than two minutes, but it cannot be performed so quickly as to enable one to see any considerable portion of the crystal violet still in transit in the stroma. The same experiment performed on a normal guinea pig not deficient in vitamin C yields precisely similar results (table 6). When this experiment is done on a guinea pig lacking in vitamin C, the dye is found on first examination to be mainly in the stroma. In order to obtain the same distribution of the dye in the deficient as in the normal animal, it is necessary to wait ten to fifteen minutes after intravenous injection of the dye before removing the tissues for examination. If ascorbic acid is injected intravenously immediately before the crystal violet, the normal picture of rapid accumulation of the dye in the epithelium is obtained. That the slow penetration of crystal violet in the vitamin C–deficient tissues is not due to any change in permeability of the stroma-epithelium barrier may be demonstrated as follows:

Two freshly excised pieces of ciliary body, one from a normal and one from a vitamin C–deficient guinea pig, are placed on a slide, and a minute drop of crystal violet solution is brought into contact with the epithelium of each specimen. The epithelium rapidly takes up the stain. If these tissues are observed aerobically, the dye is seen to remain in the epithelium, but if they are observed under nitrogen or cyanide asphyxia (under these conditions the ionic electric current in the tissues is inhibited), the dye slowly penetrates into the stroma equally in the two specimens.

In summary, the ionic electric current, as exemplified by the movement of basic dyes in the tissue, is greatly reduced in intensity in the absence of ascorbic acid, but is not entirely absent even in extreme scurvy. The persistence of a small residual interaction between stroma and epithelium even in vitamin C–deficient animals is thus confirmed.

D. TRANSFER OF WATER

In the previous paper it was shown that the passage of an ionic electric current through the ocular tissues is accompanied by the transfer of water and that the ionic electric current postulated as present in the tissues has the proper direction to carry water from stroma to epithelium, i. e. in the direction of the normal secretory flow. No quantitative relations could, however, be asserted, and no conclusions were drawn as to whether the postulated mechanism accounted for a

trivial or an important component of the water transfer. The possibility of inactivating and reactivating the secretory mechanism by deprivation or administration of ascorbic acid enabled us to test directly the contribution of this mechanism in respect to the transfer of water.

Owing to the small volume of guinea pig eyes it was necessary to construct a special manometer with which to measure the intraocular pressure with a minimal displacement of fluid being required to register a reading. The apparatus prepared (fig. 2) is a modification of the familiar compensating manometer. The diameter of the narrow portions of glass capillaries *AB* and *CD* is 0.25 mm. The remaining glass connections have an internal diameter of 1 mm. The lower portions of the instrument are filled with mercury. By turning the screw clamp

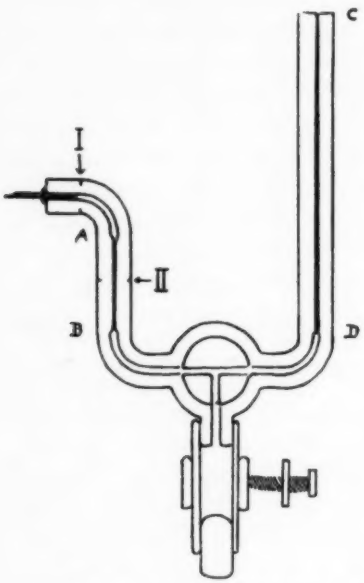

Fig. 2.—Manometer used to measure the intraocular pressure.

over the rubber tube, the position of the mercury meniscus can be adjusted to any desired level. In practice the mercury is first made to fill the manometer up to the needle. The tip of the needle is then immersed in a drop of Ringer's solution, and the mercury is allowed to drop back to the mark *I*, the tube from *I* to the tip of the needle being filled with Ringer's fluid. The stopcock is now turned so as to prevent further movement of the mercury and the needle introduced into the anterior chamber of the guinea pig (intraperitoneal ethyl carbamate anesthesia being used, with 1.25 Gm. of the drug per kilogram, plus conjunctival instillation of 0.5 per cent pontocaine hydrochloride).

When the apparatus has been rigidly fixed in place, the stopcock is turned so as to be open all three ways. If the meniscus tends to move from position *I*, it is brought back by a turn of the screw clamp. The pressure is measured by the position of the free meninscus in *CD;* the level corresponding to zero pressure is determined at the end of the experiment without changing the tilt of

the manometer. After the pressure has been recorded for five to ten minutes, the screw clamp is turned so as to bring the meniscus down to position *II*. The volume of fluid withdrawn from the eye by this procedure is the volume of the tube between *I* and *II* and amounts to 17 cu. mm. This is approximately one-third to one-half the volume of the anterior chamber in an adult guinea pig, and its withdrawal results in a marked drop in intraocular pressure. The meniscus is now kept at position *II* by continuous manual adjustments of the screw clamp, and the return toward normal of the intraocular pressure can be observed by readings of the mercury level in *CD*.

In each experiment a sample of aqueous for indophenol titration was withdrawn from one eye immediately prior to insertion of the manometer cannula in the other eye. If ascorbic acid was injected intravenously during the course of the experiment, a similar sample was withdrawn from the second eye at the end of the experiment. Figure 3 shows the result of a series of experiments of this type.

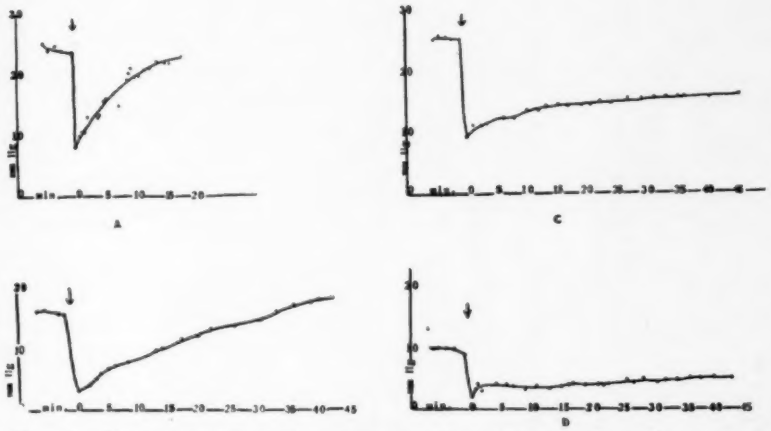

Fig. 3.—Return of intraocular pressure after withdrawal of 17 cu. mm. of aqueous from the eyes of guinea pigs. In the experiments represented by *A* and *B* the animal was normal, and in those represented by *C* and *D* the animal had been for two weeks and ten days, respectively, on a vitamin C–deficient diet. The concentration of ascorbic acid in the aqueous of the opposite eye was, in milligrams per hundred cubic centimeters, as follows: *A*, 11; *B*, 16; *C*, 0, and *D*, 0.

The normal intraocular pressure of guinea pigs under the conditions of the experiments was found to lie between 15 and 25 mm. of mercury. No significant differences in pressure were found between normal and vitamin C–deficient animals. In normal animals the withdrawal of intraocular fluid and consequent lowering of intraocular pressure was followed by rapid recovery, the pressure reaching the previous normal level in ten to twenty minutes and generally overshooting that level (reactive hypertonia). In animals deficient in ascorbic acid, the return to normal pressure was, by comparison, painfully slow. Most characteristic was the difference in the shape of the recovery curve for the two types of animals. In the normal animal the recovery of intraocular

TABLE 3.—*Reduction of Indicator Dyes in the Ciliary Body of Guinea Pigs (Ethyl Carbamate Anesthesia)*

Dye	Vitamin C Saturated				Vitamin C Deficient				Scorbutic Animals Immediately After Administration of 50 Mg. of Ascorbic Acid			
	Aerobic		Cyanide E and S	Nitrogen E and S	Aerobic		Cyanide E and S	Nitrogen E and S	Aerobic		Cyanide E and S	Nitrogen E and S
	E	S			E	S			E	S		
Bindschedler's green	.....	.....	.....	.....	++++	.....	.....	.....	++++	.....	.....	.....
2,6-dichlorophenolindophenol	++++	.....	.....	.....	+++	.....	.....	.....	+++	.....	.....	.....
Toluylene blue	++	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
Indigo trisulfonate	.....	++++	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
Indigo disulfonate	.....	+++	++++	.....	.....	.....	.....	.....	.....	.....	.....	.....
Indigo monosulfate	.....	0	+++	.....	.....	.....	.....	.....	.....	.....	.....	.....
Phenosafranine	.....	.....	0	.....	.....	.....	.....	.....	.....	.....	.....	.....
Safranine, bluish	.....	0	0	++++	.....	+++	+++	++++	.....	+++	+++	++++
Neutral red	.....	.....	.....	0	.....	0	0	0	.....	0	0	0

pressure began almost immediately with a steep rise, which gradually flattened out, yielding a curve convex upward in its whole extent. In the deficient animal the onset of recovery developed slowly, and little change in pressure might take place in the first ten minutes. The rise, when it finally occurred, was a gradual one, almost linear at first but flattening out as the normal level was approached.

In these, as in the previously reported experiments, special precautions were required to insure the presence of an effectively high concentration of ascorbic acid in the ocular tissues in the "normal" animals. In general, these animals received, in addition to a full diet, an injection of 50 mg. of ascorbic acid two to four hours before the experiment. Animals previously on a deficient diet could be made to show a normal recovery curve of the intraocular fluid if a large dose of ascorbic acid was administered immediately prior to the ethyl carbamate anesthesia.

TABLE 4.—*Reduction of Indicator Dyes in the Ciliary Body of Cats* *

	E'_o of Dye at p_H 7.4	Aerobic		Cyanide E and S	Nitrogen E and S
		E	S		
Toluylene blue	+0.101	++++	++++	++++	++++
Lauth's violet	+0.050	++++	++++	++++	++++
Methylene blue	−0.002	+++	++++	++++	++++
Indigo disulfonate	−0.143	.....	++	.....	.....
Cresyl violet	−0.175 (?)	0	.....	++++	.....
Safranine, bluish	−0.270	0	0	0	++++
Neutral red	−0.340	0	.....	0	+++
Sulfonated rosindone	−0.395	0	0	0	+

* Soluble pentobarbital anesthesia.

If, on the other hand, animals deficient in vitamin C were first anesthetized with ethyl carbamate and then given a saturating dose of ascorbic acid, the recovery curve of intraocular fluid was deficient. This failure to reestablish the normal relations on addition of ascorbic acid stands in sharp contrast to the results of the previously reported experiments, in which it was found that the addition of ascorbic acid brought a prompt return to normal of the tissue potentials and of the ionic electric current. The previous experiments had been done with the animals under ether anesthesia, whereas this could not be used for the fluid flow experiments because of the instability of the blood pressure during inhalation anesthesia. The local use of pontocaine hydrochloride in the flow experiments was found to be without effect in this regard.

In order to discover whether the conflict between these several sets of experiments was due to the difference in the general anesthetic used, we repeated and extended the studies on tissue potentials and dye transfer in normal and in vitamin C–deficient animals under ethyl

carbamate instead of ether anesthesia. The results are shown in tables 3, 4 and 6. In normal animals no difference was found between ether and ethyl carbamate anesthesia in respect to tissue potentials or dye transfer. With ether anesthesia vitamin C deficiency results, as noted, in a pronounced, but not complete, disappearance of the respiratory interchange between epithelium and stroma and in a pronounced, but not complete, disappearance of the selective transfer of acid and basic dyes. With ethyl carbamate anesthesia vitamin C deficiency results in a complete disappearance of both these activities of the secretory mechanism. With ether anesthesia the intravenous injections of ascorbic acid in a C–deficient animal resulted in a prompt return to normal of tissue potentials and dye transfer. With ethyl carbamate anesthesia the injection of ascorbic acid was without immediate effect. The catalyzed aerobic oxidation of ascorbic acid in the stroma, which was demonstrated with the aid of cyanide on normal animals under ether anesthesia and on C–deficient animals immediately after intravenous injection of ascorbic acid, was observed also in normal animals under ethyl carbamate anesthesia but was lacking in C–deficient animals under ethyl carbamate anesthesia after injection of ascorbic acid. These differences could not be attributed to a failure of ascorbic acid to reach the tissues under ethyl carbamate anesthesia, since the appearance of this substance in the intraocular fluid after intravenous injection was readily demonstrable by indophenol titration.

It follows that the normal operation of the secretory mechanism requires the presence in the tissues of some other substance in addition to ascorbic acid, a substance which is present in normal animals under either ether or ethyl carbamate anesthesia but is absent in C–deficient animals under ethyl carbamate but not under ether anesthesia. Furthermore, it is evident that this substance when present is able to catalyze the auto-oxidation of ascorbic acid. The nature of this activator of ascorbic acid oxidation is the subject of current studies.[16a]

The fact that approximately normal intraocular pressure can be maintained in the absence of ascorbic acid is not surprising. The pressure in the eye is maintained by a balance between the activities of the secretory and of the reabsorptive mechanism. We have already shown [17] that the reabsorptive mechanism is under the control of vasomotor reflexes and that it automatically compensates for the increased rate of formation of intraocular fluid which results from hyperemia of the intraocular tissues or from increased arterial blood pressure. The

16a. Friedenwald, J. S., and Buschke, W.: Role of Epinephrine in Formation of Intraocular Fluid, Am. J. Ophth. **24**:1105, 1941.

17. Friedenwald, J. S., and Pierce, H. F.: Circulation of Aqueous: Mechanism of Reabsorption of Aqueous, Arch. Ophth. **8**:9 (July) 1932.

results of the experiments just reported indicate that the reabsorptive mechanism can compensate equally well for a decrease in the rate of formation of the intraocular fluid. It is only by testing the rate of formation of intraocular fluid at subnormal pressure, at which the reabsorptive mechanism is necessarily almost completely inactivated in both normal and vitamin C–deficient animals, that the difference in the rate of formation of the fluid can be exhibited.

In summary, the mechanism of secretion of intraocular fluid in guinea pigs requires for its normal operation the presence of ascorbic acid in the tissues. In this mechanism ascorbic acid occupies the role of a mediator in a redox chain connecting the oxidase activity of the epithelium with the dehydrogenase activity of the stroma. When the oxidation-reduction interaction between stroma and epithelium is suppressed by the deprivation of this mediating substance, the rate of transfer of water is greatly reduced. The transfer of electrons, ions and water across the stroma-epithelium barrier in the ciliary body is thus shown to be a coordinated process, and the previously postulated mechanism of secretion is seen to account for all or most of the secretory activity. In order that ascorbic acid may participate in the secretory mechanism it is necessary that a certain other substance be present. This accessory, or activating, substance has in cyanide poisoning the power of catalyzing the oxidation of ascorbic acid.

IV. MECHANISM OF STORAGE OF ASCORBIC ACID

In section II it was shown that ascorbic acid is normally present in the interstitial tissue of the ciliary stroma in a concentration of 0.003 molar. This is many times greater than the normal concentration of ascorbic acid in the blood. Between these two regions of disparate concentration the only visible barrier is the capillary wall. Capillaries in many other organs certainly do not excrete ascorbic acid. An explanation for the extravascular accumulation of ascorbic acid in the ciliary stroma seemed a necessary prerequisite to any attempt to understand the intraocular secretion of this substance. Since the interstitial ascorbic acid disappears in scurvy and increases after intravenous injection of ascorbic acid, we conclude that it is derived from the blood. It follows either that cellular energy is expended to maintain the disparity of concentration or that a mechanism exists for the binding of ascorbic acid and for its local storage in nondiffusible form. To test these possibilities the following experiment was performed:

The ciliary processes of beef eyes, carefully blotted dry to avoid contamination with aqueous and vitreous, were excised and collected in a centrifuge tube. From about 50 eyes approximately 10 cc. of material can be collected. This was centrifuged at high speed, yielding a supernatant volume of 1.0 cc. of tissue juice. This fluid contained approximately 28 mg. per hundred cubic centimeters of

ascorbic acid as determined by dichlorophenolindophenol titration. To 0.8 cc. of tissue juice 3.2 cc. of absolute alcohol was added. A precipitate occupying a volume of 0.08 cc. was obtained, with a supernatant volume of 3.65 cc. The supernatant fluid was decanted and mixed with an equal volume of 8 per cent sulfosalicylic acid. A slight precipitate was separated by centrifuging and the fluid titrated for ascorbic acid with dichlorophenolindophenol, yielding a concentration 2.8 mg. per hundred cubic centimeters of ascorbic acid. The 0.08 cc. of sediment was similarly treated with 0.08 cc. of sulfosalicylic acid solution and recentrifuged and the supernatant fluid titrated, yielding a concentration of 11 mg. per hundred cubic centimeters of ascorbic acid. To refer back to the alcohol precipitation, it is plain that the concentration of ascorbic acid in the alcoholic sediment was approximately four times that in the alcoholic supernatant fluid. Repetition of this experiment on other samples of ciliary tissue juice yielded always a higher concentration of ascorbic acid in the alcohol sediment than in the supernatant fluid, the ratios being between 2:1 and 4:1.

Control experiments in which ascorbic acid was added to blood serum in a concentration of 20 mg. per hundred cubic centimeters and four volumes of alcohol added to one volume of serum, the resultant precipitate and supernatant fluid being treated as before, yielded an equal concentration of ascorbic acid in precipitate and in supernatant fluid. Both free ascorbic acid and sodium ascorbate are readily soluble in 80 per cent alcohol.

This experiment showed that ascorbic acid is present in the tissue fluid of the ciliary body at least in part as a component of an alcohol-precipitable complex. What is the nature of this binding process? In section III–A it was noted that the capacity of young guinea pigs to store ascorbic acid in the ciliary body is extremely feeble as compared with that of adult guinea pigs or of rabbits. This difference between young and old guinea pigs furnished a possible experimental approach to the problem. We have sought for some other difference between the tissue of young and of adult animals which might be correlated with the capacity to store ascorbic acid.

If an acid dye of large molecular weight, such as bromphenol blue or rose bengal, is injected intravenously into a rabbit, the blood plasma immediately becomes heavily colored by the dye, and the dye appears promptly in the stroma of the ciliary body. These dyes are rapidly excreted by the kidneys or liver or both, and the color disappears from the blood plasma in thirty to sixty minutes after injection. In spite of its rapid elimination from the blood, the dye remains in the stroma of the ciliary body and is visible in eyes enucleated twenty-four hours after the injection. Similarly bound dye is seen in the mucosa of the small intestine, the choroid plexus, certain portions of the skin and some other organs. Similar experiments on adult guinea pigs yield similar results. The dye persists in the stroma of the ciliary body long after it has disappeared from the blood. In young guinea pigs (200 Gm. body weight) the dye appears in the stroma of the ciliary body as promptly and in almost as high concentration as it does in adults. As

in older animals or in rabbits, the dye fails to penetrate the epithelium and hence can leave the ciliary stroma only by diffusing back into the blood. One hour after injection the dye is no longer visible in either the blood plasma or the ciliary stroma. It is evident that the ciliary stroma of the adult guinea pig and of the adult rabbit (young rabbits were not tested) contains an acidophilic substance capable of binding acid dyes and that this substance is lacking or ineffective in the tissues of the young guinea pig. In order to test the relation of this acidophilic tendency to the capacity to bind ascorbic acid, the following experiment was performed:

The ciliary body and iris of each eye of an albino rabbit were placed in two small vessels together with 5 cc. of sodium chloride solution. Five milligrams of sodium cyanide was added to each vessel in order to suppress the secretory transfer of dye. One hundred milligrams of sodium ascorbate dissolved in 2 cc. of distilled water was added to one vessel and a corresponding amount of distilled water to the other. Finally a small amount of a dilute solution of rose bengal was added, an equal amount to each vessel. The dye was so dilute as to be barely visible in thin layers of the fluid. Its visible presence in the tissue could thus be due only to active staining of the tissue. Samples were removed from time to time for observation. The dye was taken up by the tissue slowly. At the end of two hours, however, the specimen without added ascorbic acid was diffusely stained, the epithelium and the stroma having taken up the dye in equal intensity. On the other hand, the specimen with the large addition of ascorbic acid showed the epithelium to be well stained, while in the stroma the color was no more intense than in the bathing fluid.

This experiment showed that the acidophilic substance in the ciliary stroma exhibits a certain degree of specificity in its capacity to bind ascorbic acid and that ascorbic acid and certain acid dyes can displace one another from the tissue. The same result may be obtained with the intact animal as follows:

Two adult albino guinea pigs of equal size and age were placed on diets of which one was abundant in vitamin C and the other deficient in vitamin C. On the seventh and eighth days the "normal" animal received an injection of 100 mg. of ascorbic acid in order to saturate its tissues with this substance. On the eighth day each animal received an intravenous injection of 50 mg. per kilogram of rose bengal dissolved in salt solution. One hour after the injection, one eye of each animal was removed and the ciliary body examined. The ciliary stroma of the scorbutic animal was diffusely stained with the dye. In the animal saturated with ascorbic acid, some dye was visible in the stroma, but more was to be seen within the blood vessels. After another hour the second eye was removed and the animals killed. The scorbutic animal showed almost as much dye in the ciliary stroma as it had an hour before. In the vitamin C–saturated animal, dye was no longer visible in the ciliary body. An examination of other organs revealed interesting contrasts. The mucosa of the small intestine of the scorbutic animal was deeply stained, while that of the saturated animal showed only a feeble color. On the other hand, the subcutaneous tissues of both animals were stained almost equally.

It is evident that the acidophilic components of various tissues differ from one another in their capacity to bind ascorbic acid. Presumably the binding substance is a protein which, while not necessarily basic, at least contains a large number of free basic groups.[18] We have no data on the physicochemical characteristics of the ascorbic acid complex, but it is evident that it may at least constitute a further link in the redox chain that we have been studying.

In summary, ascorbic acid is stored in the stroma of the ciliary body by being reversibly bound to an acidophilic substance.

V. INTRAOCULAR SECRETION OF ASCORBIC ACID

The present investigation was initially undertaken with a view to discovering whether the mechanism which we had previously postulated to explain the secretion of the intraocular fluid was capable also of explaining the intraocular secretion of ascorbic acid. The cardinal facts to be explained in respect to the intraocular accumulation of ascorbic acid are: (*a*) that ascorbic acid is present in the aqueous fluid (in some animal species) in apparently freely diffusible, unbound form in a concentration ten to twenty times that in the blood[19]; (*b*) that the ascorbic acid concentration in the aqueous rises and falls with similar variations in the ascorbic acid concentration in the blood[20]; (*c*) that ascorbic acid disappears from the aqueous if the lens is removed or damaged, as in naphthalene poisoning[21]; (*d*) that the normal lens but not the naphthalene-poisoned lens is capable in vitro of reducing dehydroascorbic acid to ascorbic acid.[22] Previous attempts to explain these phenomena are as follows:

1. It has been suggested that ascorbic acid is synthesized by the lens.[23] This theory fails to account for (*b*).

2. It has been suggested that ascorbic acid is secreted in reduced state by the ciliary body.[24] This theory fails to account for (*c*) and (*d*).

3. It has been suggested that dehydroascorbic acid enters the ocular cavity by diffusion from the blood and is reduced to ascorbic acid by the lens[22] and that the escape of the reduced form is relatively impeded

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18. The protein of the crystalline lens is acidophilic at neutral p_H, binds ascorbic acid and contains a large number of diamino acids, but has its isoelectric point on the acid side of neutrality.

19. Müller, H. K.: Arch. f. Augenh. **108**:41, 1934.

20. Goldmann, H., and Buschke, W.: Arch. f. Augenh. **109**:314, 1934.

21. Bietti, G.: Boll. d'ocul. **14**:3, 1935. Müller and Buschke.[2]

22. Müller, H. K., and Buschke, W.: Arch. f. Augenh. **108**:592, 1934.

23. Fischer, F. P.: Klin. Wchnschr. **3**:596, 1934. Müller, H. K.: Arch. f. Augenh. **109**:434, 1935.

24. Bonsignore, A.: Boll. Soc. ital. biol. sper. **10**:505, 1935. Ciotola, G.: Boll. d'ocul. **15**:740, 1936.

by the blood-aqueous barrier.[25] The conception of a diffusion of dehydroascorbic acid from blood to aqueous involves assumptions regarding the stability and the concentration of this substance in the blood which are now known to be incorrect. As will be shown, ascorbic acid escapes from the aqueous at about the same rate as dextrose. Nevertheless, the central point of this theory—that ascorbic acid may enter the aqueous in oxidized form—is supported by our present studies, since we have found a source of oxidation of ascorbic acid in the secretory organ.

Ball[7] has shown that at physiologic p_H dehydroascorbic acid is undissociated and hence electrically neutral in solution. Furthermore, dehydroascorbic acid undergoes spontaneous irreversible rearrangement, becoming transformed into a substance no longer active as a vitamin. At physiologic p_H the half-life of dehydroascorbic acid in vitro, according to Ball, is two minutes.

If part of the ascorbic acid was present unbound in the reduced form in the ciliary stroma, the ionic electric current would inhibit the penetration of this anion from stroma to epithelium. In its role as mediator, ascorbic acid is continually being oxidized. The possibility of complex formation being excluded for the moment, three possible fates may overtake the dehydroascorbic acid: (*a*) it may be reduced by the other mediators present in the stroma or by the stroma cells, (*b*) it may undergo irreversible change and be lost from view or (*c*) it may as an electrically neutral substance diffuse into the epithelium, or be carried into the epithelium by the current of the secretory fluid. The last-mentioned process would be facilitated if, as we have suggested, the oxidation of the ascorbic acid took place at the surface of the stroma-epithelium barrier. We have at present no knowledge as to how dehydroascorbic acid may be stabilized in the epithelial cells or as to how its back diffusion into the stroma may be prevented, but we can subject to experimental test the questions: Does ascorbic acid reach the aqueous through the ciliary body? What is the rate of disappearance of ascorbic acid from the aqueous, and hence what is the rate of intraocular secretion? Is oxidation of ascorbic acid necessary for its intraocular secretion?

Since the concentration of ascorbic acid is high both in the aqueous and in the stroma of the ciliary body, the question might be raised whether ascorbic acid reaches the ciliary stroma from the blood, as has been postulated, or reaches the aqueous through some unknown portal and enters the ciliary body from the intraocular cavity. In order to answer this question it was first necessary to know how long a time

25. Monjukowa, N. K., and Fradkin, M. J.: Arch. f. Ophth. **133**:328, 1935. Goldmann and Buschke.[20]

must elapse between intravenous injection of ascorbic acid and a rise in the concentration of ascorbic acid in the aqueous.

In a series of experiments, aqueous was withdrawn from one eye of a rabbit for indophenol titration. An intravenous injection of 250 mg. of ascorbic acid per kilogram of body weight was then made. In different animals fluid was withdrawn from the second eye at varying intervals after the intravenous injection.

It was found that in rabbits the first measurable rise in the ascorbic acid content of the aqueous occurred about ten minutes after intravenous injection and that the maximum rise, amounting to between a onefold and a twofold increase, was reached between forty-five minutes and one hour after injection.[26] It was evident that if an increase in the ascorbic acid content of the ciliary epithelium could be demonstrated within five minutes after the injection it would be proved that ascorbic acid reaches the epithelium from the ciliary stroma and not from the intraocular fluid.

One eye of an albino rabbit was removed and bisected at the equator. The lens and the vitreous were gently removed from the anterior segment, and the belly of a scalpel was used to scrape the surface of the ciliary process. The scrapings, suspended in a drop of Ringer's solution on a microscope slide, were seen to consist of sheets of epithelium. One such preparation was allowed to dry in air, and a second was dried under an atmosphere of nitrogen. When the scrapings had been firmly dried onto the slides, a solution of 10 per cent silver nitrate was added to each slide without exposure to light and without admission of oxygen to the second specimen. After five minutes the second specimen was removed from the nitrogen chamber, and, still in the dark, both specimens were treated with 10 per cent sodium thiosulfate. After they had been two minutes in this solution light could be admitted without disadvantage. The smears were washed, dried and examined under oil immersion with the microscope. Neither specimen contained an appreciable amount of precipitated silver, but a few granules were to be seen in the specimen dried under nitrogen.

An intravenous injection of ascorbic acid, 250 mg. per kilogram of body weight, was now made into the same rabbit, and two minutes after completion of the injection (two and one-half minutes after it was begun) the second eye was removed and rapidly opened. Scrapings were made from the ciliary processes and treated like those from the first eye. In the specimen dried under nitrogen, a heavy silver stain was produced. In the specimen dried in air, silver granules were found on the surface of the epithelial cells but not in the interior of the cells.

The results of these experiments show that ascorbic acid injected intravenously reaches the ciliary epithelium before there has been an appreciable increase of reducing substance in the aqueous, and, hence, that the immediate source of the ascorbic acid in the aqueous is the ciliary body.

The disappearance of ascorbic acid from the anterior chamber may be studied by introducing into the anterior chamber a high concentration

26. These results are in agreement with the results of similar experiments of Goldmann and Buschke.[20]

of ascorbic acid and reexamining the fluid after a given time to determine how much remains.

The procedure used was that of Kronfeld as modified by Friedenwald and Pierce,[27] special care being taken to avoid traumatic irritation of the eye. Isotonic solutions of ascorbic acid and sodium chloride were mixed with the aqueous and a sample of the initial concentration obtained. Subsequently a second sample was withdrawn for comparison. In view of the considerable scattering of the results, a large number of experiments (38) were performed. Since the normal concentration of ascorbic acid in the rabbit's aqueous is approximately 25 mg. per hundred cubic centimeters, this figure was subtracted from the

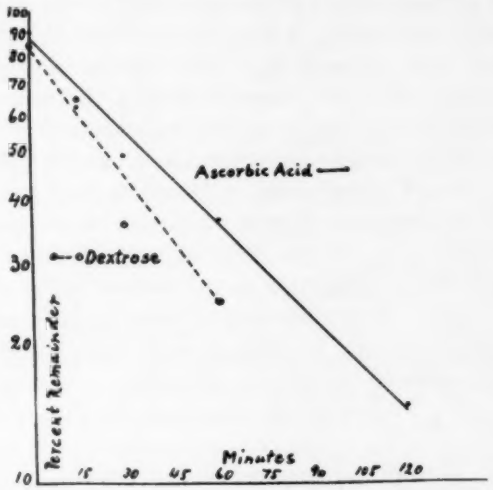

Fig. 4.—Disappearance of ascorbic acid and dextrose from the anterior chamber of the rabbit's eye.

concentrations measured in order to determine the deviation from equilibrium. Initial concentrations of 40 to 2,900 mg. per hundred cubic centimeters above normal were used.

The experiments revealed an initial disappearance of approximately 10 per cent of the injected excess of ascorbic acid. The loss may have been due to a variety of factors, including possibly certain technical errors in the experiment of no significance in relation to the present problem.[28] After this initial loss the ascorbic acid content of the aqueous approached the normal level at a rate uniformly proportional to the deviation from equilibrium (fig. 4). The rate of approach to equilibrium

27. Friedenwald, J. S., and Pierce, H. F.: Circulation of the Aqueous: Reabsorption of Crystalloids, Arch. Ophth. **10**:449 (Oct.) 1933.

28. During removal of the second sample some fluid may enter the anterior chamber from the posterior chamber and result in a slight dilution of this sample.

was not influenced by a previous injection of ascorbic acid into the anterior chamber, this fact indicating that the amount of the injected dose required to saturate the adjoining tissues was insignificant. According to these data the rate of disappearance of ascorbic acid from the anterior chamber (reabsorption plus possible loss by oxidation) amounts to roughly 0.8 per cent per minute. Similar experiments performed with dextrose gave a rate of disappearance of this substance from the anterior chamber of rabbits' eyes of roughly 1 per cent per minute. There is, therefore, no marked obstacle to the reabsorption of ascorbic acid.

Since the volume of the anterior chamber in the rabbit is 0.25 cc. and the normal concentrations of ascorbic acid in the aqueous 25 mg. per hundred cubic centimeters, it may be calculated that the amount of ascorbic acid lost from one eye of a rabbit per minute is of the order of 0.5 micrograms. For the concentration to be maintained at its normal, stationary level, an equal amount must be secreted per minute. The amount stored in the iris and ciliary body would suffice for thirty minutes at this rate of consumption. Assuming that each molecule of ascorbic acid which arrives in the aqueous has in transit contributed two electrons to the secretory electric current, we arrive at an estimated electric current of 0.01 milliampere as the minimal value attributable to the secretory current. If the amount of ascorbic acid secreted in the aqueous per minute is only a small part of that which has become oxidized in the course of its role as mediator, as is most likely, then this estimate is only a correspondingly small fraction of the secretory current.

In summary, ascorbic acid is secreted into the intraocular fluid in rabbits at a rate of approximately 0.5 micrograms per minute. It reaches the intraocular fluid immediately from the ciliary body and hence ultimately from the blood. It is present in the epithelium chiefly in oxidized form. The question as to whether oxidation of ascorbic acid is necessary for its intraocular secretion is discussed in the next section.

VI. INTRAOCULAR SECRETORY SYSTEMS WITHOUT ASCORBIC ACID

The work of a large number of investigators has shown that ascorbic acid is present in the aqueous in higher concentration than in the blood in a large number of animals, including man, the Herbivora, swine, rabbits and guinea pigs. In dogs, cats, rats and mice,[21] much lower concentrations of reducing substance are found in the aqueous. In the small rodents the measurement is difficult and fraught with error. It is possible, furthermore, that ascorbic acid is rapidly oxidized in the anterior chambers of these animals by oxygen's diffusing through their

very thin corneas. In any event, a few exploratory experiments on albino rats in respect to the indophenol oxidase reaction, the potential of the epithelium and of the stroma and the behavior of the tissue toward acid and basic dyes gave no indication that the secretory system in these animals is different from that in the animals we had already studied. Similar preliminary experiments on cats, however, raised questions leading to further studies. Unfortunately, we have been unable, so far, to obtain albino cats, and our studies of the redox potentials in the uveal tissues are therefore most incomplete.

Cats, like rabbits and many other animals, are not subject to scurvy and do not require vitamin C in their diet. Nevertheless, their blood contains titratable indophenol-reducing substance in concentrations similar to those found in rabbits. We have found the spinal fluid of cats similar in reducing power to that of rabbits. Exploratory investigations on the choroid plexus of cats in respect to indophenol oxidase reaction, apparent oxidation-reduction potential and permeability to dyes indicated that the secretory mechanism in this tissue is similar to that found in the choroid plexus of swine and of rabbits by Stiehler and Flexner [29] and similar also to that found in the ciliary body of rabbits and of guinea pigs by us. It would appear, therefore, that the blood and the spinal fluid of cats do not differ from those of rabbits in respect to ascorbic acid.

The aqueous of cats' eyes normally contains only small amounts of reducing substance, amounts comparable to those in the blood of the same animal. The reducing substance of cats' aqueous can be identified as ascorbic acid by potentiometric titration. Even after massive intravenous injections of ascorbic acid, only slight increases in the reducing substance of the aqueous take place. If, however, the aqueous is withdrawn from one eye and immediately afterward an intravenous injection of ascorbic acid made, then the concentration of ascorbic acid in the plasmoid aqueous formed during the period of high blood ascorbic acid content is found to be much higher than the concentration in the aqueous of the undisturbed eye. Not only does the blood-aqueous barrier normally fail to secrete ascorbic acid into the eye, but the transport of this substance is evidently impeded unless the barrier is disturbed so as to allow ingress also of plasma proteins. Failure to secrete ascorbic acid into the intraocular cavity is not due to an absence of this substance from the ciliary body (table 1).

Following the now familiar pattern of our studies, we investigated first the behavior of the tissue toward acid and basic dyes. Crystal violet (basic dye) when injected intravenously appears promptly in the epithelium, of which the superficial layer is free from pigment and

29. Stiehler, R. D., and Flexner, L. B.: J. Biol. Chem. **126**:603, 1938.

in which the dye can readily be detected. Bromphenol blue (acid dye) injected intravenously does not appear in the epithelium, though teased specimens show abundant dye in the stroma. If the tissue is poisoned with cyanide, bromphenol blue appears in the epithelium. Tests for the transport of dyes from epithelium to stroma could be made as follows:

Excised portions of iris and ciliary body from a cat's eye were placed on glass slides and a drop of dye brought in contact with the epithelium. The possible penetration of the dye into the stroma could not be observed on account of the heavy pigmentation of the tissue. After varying intervals, the diffusion of the dye in different samples of tissue was stopped by dropping of the tissue into ether that had been cooled with solid carbon dioxide to approximately — 70 C. The tissue froze almost instantaneously. The frozen tissue was then dehydrated by vacuum distillation at subzero temperature according to the method of Gersh,[30] embedded and sectioned.

The results revealed that bromphenol blue (acid dye) was rapidly transferred from epithelium to stroma, whereas crystal violet (basic dye) remained exclusively in the epithelium under normal conditions and penetrated slowly into the stroma under cyanide asphyxia. It is clear that there is no striking difference between cat and rabbit with respect to the transport of acid and basic dyes in the ciliary body.

The apparent redox potential of the nonpigmented superficial layer of epithelium can be studied in the usual manner. Under aerobic conditions the cells reduce toluylene blue and Lauth's violet completely (tables 4 and 5). Methylene blue is strongly but not completely reduced. With the first two dyes the color is restored, and with the last it is increased, by addition of ferricyanide. It follows that the apparent redox potential of the ciliary epithelium in the cat is 0.1 volt more negative than that of the rabbit.

The apparent redox potential of the ciliary stroma in the cat can be estimated by injecting a test indicator intravenously and then teasing the ciliary body on a glass slide while observing it under a microscope. The dye may be immediately visible at the torn surface. If ferricyanide is added, the reduced dye, if present, is oxidized. It is to be admitted that this procedure introduces new sources of error. Nevertheless, safranine bluish was found to be partially reduced in the cat's ciliary stroma by this means. Similar teasing of a rabbit's ciliary body containing safranine did not result in reduction of the dye. Furthermore, safranine appears promptly in the cat's ciliary epithelium after intravenous injection, the cat resembling in this respect the vitamin C–deficient guinea pig and differing from the normal guinea pig and from the rabbit.[31] Control experiments on pigmented rabbits showed

30. Gersh, I.: Anat. Rec. **53**:309, 1932.

31. The leuko base of this safranine dye is undissociated at physiologic p_H.

that these do not differ in apparent potential from albino rabbits. The peculiarity found in cats is not due to our failure to obtain albino animals.

The low potential of the epithelium was further supported by tests with the indophenol oxidase reagent. With this reagent the cat's ciliary epithelium shows only a feeble stain. No stain appears in the stroma. The intensity of this stain is not increased by soaking the tissue for five minutes in 0.001 molar ferricyanide in Ringer's solution and then wash-

TABLE 5.—*Estimated Apparent Redox Potentials in the Ciliary Body*

(Volt, p_H 7.4)

	Aerobic		Cyanide	Nitrogen
	E	S	E and S	E and S
Rabbit	+0.100	−0.130	−0.200	−0.290
Guinea pig (ether anesthesia)				
Vitamin C saturated	+0.100	−0.160	−0.200	−0.290
Vitamin C deficient	+0.175	−0.260	−0.275	−0.290
Scorbutic, given vitamin C	+0.100	−0.160	−0.200	−0.290
Guinea pig (ethyl carbamate anesthesia)				
Vitamin C saturated	+0.100	−0.160	−0.200	−0.290
Vitamin C deficient	+0.175	−0.275	−0.275	−0.290
Scorbutic, given vitamin C	+0.175	−0.275	−0.275	−0.290
Cat	−0.015	−0.140	−0.230	−0.370

TABLE 6.—*Transfer of Acid and Basic Dyes in the Ciliary Body* *

	Crystal Violet		Bromphenol Blue	
	Epithelium to Stroma	Stroma to Epithelium	Epithelium to Stroma	Stroma to Epithelium
Guinea pig (ether anesthesia)				
Vitamin C saturated	0	++++	++++	0
Vitamin C deficient	0	+++	+++	0
Scorbutic, given vitamin C	0	++++	++++	0
Guinea pig (ethyl carbamate anesthesia)				
Vitamin C saturated	0	++++	++++	0
Vitamin C deficient	+	+	++	++
Scorbutic, given vitamin C	+	+	++	++

* 0 indicates no penetration; +, slow diffusion; ++, rapid diffusion; +++, slow accumulation beyond diffusionn; ++++, rapid accumulation beyond diffusion.

ing it briefly in Ringer's solution before testing with the indophenol reagent. It is evident that the feeble indophenol oxidase reaction is not due to the low potential of the tissue, but rather that the cat's ciliary epithelium is relatively poorly supplied with some component of the indophenol oxidase system and hence has a lower potential than that of the rabbit.

It is evident that the general pattern of the secretory mechanism in the ciliary body of the cat resembles that in the other animals we have studied. There is a difference in redox potential between the epithelium and the stroma which is available to do work. This difference in potential is attributable to a difference between the two tissues in

distribution of the respiratory enzymes. The irreciprocal permeability of the tissues to acid and basic dyes reveals the interaction between stroma and epithelium. The potential levels of both tissues, however, are so negative that ascorbic acid is kept reduced in both. This substance is incapable, therefore, of acting as a mediator in this secretory system. The nature of the mediator which serves in its stead has not been explored. In the absence of oxidation of ascorbic acid in the cat's ciliary body, this substance is not secreted into the intraocular cavity.

In summary, the secretory mechanism in the cat's ciliary body is constructed similarly to that of the rabbit and of the guinea pig. However, both the epithelium and the stroma of this tissue generate oxidation-reduction potentials which are substantially below the normal potential of ascorbic acid. Consequently ascorbic acid is unable to act as mediator in this system. Though ascorbic acid is present in the ciliary stroma of the cat in amounts comparable to those in the other species studied, ascorbic acid is not secreted into the intraocular fluid of the cat in appreciable amounts.

VII. COMMENT

In the previous paper, studies were reported on the secretory mechanism of the ciliary body of rabbits, and a theory was formulated which was shown to be capable of explaining and ordering the known facts. It would seem well to review at this point what parts of this theory were supported by direct experimental evidence and what parts were postulated in order to complete the theory.

It was shown that a difference in redox potential exists between epithelium and stroma in the ciliary body. It was shown that a barrier exists between stroma and epithelium which contains as one of its components a substance capable of reversible oxidation and reduction. It was postulated that oxidation-reduction interaction takes place between stroma and epithelium, the stroma-epithelium barrier acting as mediator between these tissues. It follows from this postulate that electrons and cations may be transferred from stroma to epithelium and anions from epithelium to stroma. It was found that dyes which were anions, cations or uncharged molecules penetrated the tissue in the manner predicted. This evidence proved that interaction between stroma and epithelium may take place. In the present paper, experimental evidence is presented showing that oxidation of the stroma by the epithelium does, in fact, take place.

In the previous paper it was shown that the barrier between stroma and epithelium is negatively charged and that the passage of an ionic electric current through this membrane was accompanied by a transfer of water by electro-osmosis. It was postulated, therefore, that the

secretory movement of water across the membrane was accomplished by the electric current generated through the interaction of stroma and epithelium. In the present paper the dependence of the movement of water into the eye on the interaction between epithelium and stroma is shown to be directly observable. With these two postulated features replaced by experimental observations, the hypothesis regarding the mechanism of secretion which we have formulated has been completely confirmed.

In the present paper, this hypothesis is further expanded (fig. 5). It is shown that the interstitial tissue of the ciliary stroma contains substances capable of reversible oxidation-reduction which act as mediators in the oxidation-reduction interaction between stroma and epithelium, occupying the portion of the chain of interacting substances between the stroma-epithelium barrier, on the one hand, and the stroma cells on the other. One of these mediating substances has been identified

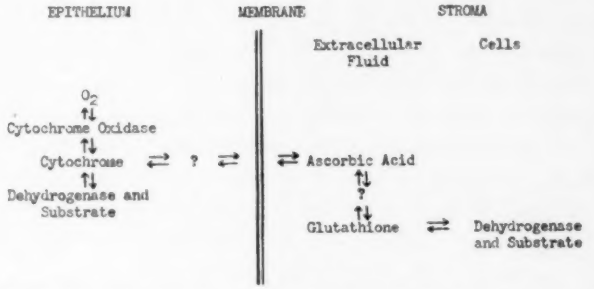

Fig. 5.—Schematic representation of redox chains in the ciliary body.

as ascorbic acid. This appears to be the most readily oxidizable of the stroma mediators and, hence, may provisionally be assigned the role of the chief substance to be oxidized directly by the stroma-epithelium barrier. With the identification of ascorbic acid and the demonstration of its role in the ciliary body, the theory of the secretory mechanism begins to be concerned with substances as well as with their chemical and structural relations. It may be pointed out, however, that ascorbic acid is not always and everywhere a necessary constituent of the intraocular secretory mechanism. In cats we have found an intraocular secretory system which conforms in structural pattern to that outlined, but in which both stroma and epithelium generate potentials such that ascorbic acid would be strongly reduced in both tissues. This substance, therefore, does not and cannot act as a mediator in the secretion of the intraocular fluid of the cat.

The study of the role of a particular substance in the secretory mechanism raises fresh problems. How does the substance reach the

place of its required reaction and what is its subsequent fate? With respect to ascorbic acid both these questions have been investigated. The first problem, which concerns the mechanism of storage of ascorbic acid in the ciliary stroma, led us to discover an acidophilic component of the ciliary stroma to which the ascorbic acid is reversibly bound. The question whether this bound complex of ascorbic acid has any function in the secretory mechanism other than that of local storage of the ascorbic acid remains at present unanswered. The second problem, which concerns the mechanism of the intraocular secretion of ascorbic acid, cannot now be fully answered, but it has been shown that oxidation of ascorbic acid is a probable step in this process. Thus the mechanism of the intraocular secretion of ascorbic acid is linked with the oxidative activity of this substance.

VIII. SUMMARY

The interstitial tissue of the stroma of the ciliary processes contains a group of reducing substances, one component of which has been identified as ascorbic acid (vitamin C). These substances act as a mediating system, facilitating the oxidation-reduction interaction between the stroma cells and the stroma-epithelium barrier.

Elimination of vitamin C from the diet of guinea pigs leads to the disappearance of this substance from the ocular tissues long before any constitutional symptoms of scurvy develop. The loss of ascorbic acid from the secretory system in the eye results in a decrease in the rate of transfer of basic dyes from stroma to epithelium and in a decrease in the rate of secretion of the intraocular fluid.

Ascorbic acid is stored in the ciliary stroma, being reversibly bound by an acidophilic component of this tissue.

Oxidation of ascorbic acid by the ciliary epithelium is probably a necessary step in the intraocular secretion of this substance.

The secretory mechanism of the ciliary body in the cat conforms in pattern to that in the rabbit and in the guinea pig, but the redox potentials of both epithelium and stroma are considerably more negative than the normal potential of ascorbic acid. Consequently ascorbic acid does not act as a mediator in this system.

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DISCUSSION

DR. LUDWIG VON SALLMANN: It would certainly be interesting to view Dr. Friedenwald's work against the historical background of the dispute over the origin of the aqueous—secretion or filtrate dialysis. However, there is no need to define Dr. Friedenwald's work in the light of the old secretion theory, because he does not consider secretion in the sense of a definite glandular activity of the ciliary epithelium but in the sense of a mechanism, and these are his words: "Whereby the energy of cellular metabolism is made available for the work of water transport."

The essential statement of his work refers to the finding of a selective irreciprocal permeability of the epithelium-stroma barrier based on a mechanism which transfers basic dye stuffs and water from blood to aqueous and acidic dyes in the opposite direction. This unidirectional permeability of the ciliary body depends according to this theory on an electric current which has its origin in the differences of the oxidative and the reductive processes in the epithelium and the stroma, respectively, and is carried out by an electron transfer through the barrier presumably mediated by several reversible oxidation-reduction systems.

Dr. Friedenwald and his co-workers determined the potentials which characterize the difference in the reductive and the oxidative processes of the respective layers of the ciliary body by using one of the principles of vital and supravital staining. They had to face the objections which are advanced against the indicator method with acidic and basic dyes. Some dyes are strongly toxic; many have specific affinities to cells or parts of cells. The viscosity, the molecular size and the catalytic effect of the dyes and the time factor may also have some bearing. Moreover, in experiments in vitro, capacity and poising effects cannot be neglected. These factors may certainly interfere with the electrohistologic distribution of the dyes and must be considered in the interpretation of the results. In addition, the fact stressed by Duke-Elder that the dyes are the salts of weak acids and alkalis must be taken into account in their practical application, since their mechanism of penetration differs from that of the salts of strong acids and alkalis occurring in body fluids.

As to the first point, only a few of the numerous dyes employed by Dr. Friedenwald can be considered as toxic in the concentrations used. It is not justifiable to argue that all staining of living tissue causes damage to the substrate because of its physicochemical interaction with the cell constituents, and I believe that the demand for undue accuracy in this specialized application of vital staining—a field which in itself is not completely understood—is unwarranted.

As to specific affinities as a possible source of misinterpretation, Dr. Friedenwald and his co-workers varied the technic sufficiently to strengthen their viewpoint and regarded their data with due caution. This is also true in regard to the other objections mentioned. Unfortunately, the direct electrometric method of measurement cannot be applied to confirm the results obtained with the indicator method. The results of these two methods of estimating the potential in cells and tissue show fair agreement only under ideal conditions. It is pointless therefore to discuss the accuracy of the determined potentials, considering the limitations of the use of oxidation-reduction potential indicators. However, the potentials of ocular structures measured electrometrically change sharply in anesthesia, with injuries and in all circulatory disturbances. In Dr. Friedenwald's work no mention is made of these influences, and it would be interesting to hear his opinion on them.

The work was extended to the determination of different oxidation-reduction systems which may act as mediators in the stroma-epithelium barrier. The first system studied was the sluggish oxidation-reduction system of ascorbic acid. The investigation of this system seemed to me

one of the most comprehensive pieces of original work in this field of experimental research.

The recent contribution of Dr. Friedenwald and Dr. Buschke concerned the new problem of a humoral regulation by epinephrine, which is regarded as another mediator acting on the epithelium-stroma barrier. This work also was based on the use of dyestuffs as indicators in vivo and supravitally and, in addition, on the rate of restoration of intraocular pressure after withdrawal of aqueous. It cannot be doubted that the investigators met more difficulties than they had encountered in their previous work. The difficulties lie partly in the lack of knowledge of epinephrine deficiency. No definite symptoms attributable to this condition are known. No deficiency can be produced by adrenalectomy. On the other hand, it is unlikely that complete removal of the chromaffin tissue can be achieved by adrenalectomy in any kind of surgical approach. Furthermore, substitution for the adrenal cortex of injections of adrenal cortex extract, even in large doses, does not exclude an integral effect on the electrobiologic processes due to the disturbed cortical function. Finally, sympathin, the epinephrine-like exciting substance liberated at the adrenergic terminals, is present and acts in adrenalectomized animals. It would be valuable to learn Dr. Friedenwald's viewpoint on these questions. They deal, however, with theoretic explanations and are of minor value when the abundance of reproducible, clearcut evidence presented in his work is considered. Theories are ever changing, and it is possible that new experiments may necessitate a change, but this does not lessen the importance of the facts found by Dr. Friedenwald and his co-workers.

Their investigations are for me the most outstanding of those reported in this field of ocular physiology in the last fifteen years and I believe are of paramount significance in the problem of the formation of aqueous.

Dr. Irvin M. Korr (by invitation), New York: There are several points in Dr. Friedenwald's paper which at once attract the interest of the physiologist because of their wide applicability. Physiologists have long been seeking a mechanism for the secretion of electrolytes. Dr. Friedenwald has described such a mechanism in the eye and its activation by epinephrine. Its existence immediately raises the question of the existence of a similar mechanism in the handling of water and electrolytes by the kidney tubule under the control of the antidiuretic hormone of the hypophysis and in the movement of electrolytes in general under the influence of the adrenal cortex. I am confident that the adoption of the Friedenwald mechanism as a working hypothesis in these fields of investigation would prove fruitful. A cellular approach to the mechanism of hormonal action is also provided.

Another point of interest is the role of vitamin C. Although this substance has long been known to be capable of reversible oxidation and reduction, no place has been found for it in cellular respiration, as has been found, for instance, for vitamin B_2. It seems reasonable to assume from the work of Dr. Friedenwald and his collaborators that the role of ascorbic acid is not that of oxidative catalyst but rather that of carrier of oxidative energy from one cell to another. This question, it seems to me, deserves investigation.

Dr. Jonas S. Friedenwald: I am grateful and somewhat overwhelmed by the remarks of Dr. von Sallmann and Dr. Korr. I think it would take me a long time to answer or even to discuss many of the points that have been mentioned. I should like to call attention particularly to one point discussed by Dr. von Sallmann. Two entirely different concepts of what is called "secretion" are ordinarily confused. On the one hand there is the secretion of thyroxin by the thyroid, by which is meant the local production of a highly specific substance in the thyroid gland as the result of a highly individual local metabolism. On the other hand there is the secretion of urine and gastric juices, by which is meant mainly the transfer of water and other substances normally present in the blood across barriers from capillary to tubule. The two problems, the one of chemical synthesis and the other of transport, are from the point of view of energy and metabolism entirely distinct and cannot be approached simultaneously. So my co-workers and I have confined ourselves in this study to the problem of the transfer into the aqueous of water and of components present in the dialysates of the blood. I think that if our results have any wider significance, and I hope they have, the success we have achieved is due to the fact that we were able to study in the ciliary body examples of what might be called the simplest form of secretion, secretion in which the secreted fluid differs only in minor respects from a dialysate of the blood, secretion in which no factor of synthesis or of great difference in concentration is involved. When we try to apply the concepts derived from this simple organ to organs which transport fluids against osmotic pressure we encounter great but I hope not insuperable difficulties. Dr. Flexner, who took part in a portion of this work, especially in developing the application of our hypothesis to the choroid plexus, has made some preliminary studies on the kidney. He found that he could identify five different portions of the kidney tubules which differed from their neighbors in the concentration of cytochrome oxidase, so that even from the relatively simple point of view so far followed the kidney is composed of at least five different types of secretory organs.

One question about which I think I should say a little more is this: Can the animals on which we have done adrenalectomies and have given adrenal cortex extract and which have then been found to be abnormal but restorable to normal with epinephrine be regarded as showing a deficiency of epinephrine rather than of adrenal cortex secretion? I do not know the answer. I do not know any way of deciding what is an adequate dose of adrenal cortex extract. We know how much to give in order to make the animal survive, and that much we have given, but have we given enough to produce a normal secreting mechanism in the ciliary body of the animal? I think we cannot be sure until we know what is the normal level of adrenal cortex secretion in the body. It must be remembered that there are many functions known definitely to be controlled normally by adrenal cortex extract which are influenced temporarily by epinephrine. For instance, after adrenalectomy the blood sugar decreases and a deficiency of adrenal cortex secretion develops. The levels can be temporarily raised by injecting epinephrine. On the basis of that simple fact one

might believe that the decrease in blood sugar after adrenalectomy is due to a deficiency of epinephrine, but it is known that adrenal cortex secretion itself has an effect on the blood sugar as important as that which can be achieved by epinephrine. I can only say that we have given huge doses of adrenal cortex extract which have not affected the secreting mechanism of the ciliary body. We cannot increase the doses of adrenal cortex extract more than we already have done for the reason that even the most potent preparations of the cortical hormone are contaminated with epinephrine, and if we gave ten times as much of the extract as we have done, we would begin to reach levels of epinephrine absorption which would be effective. We believe that we have gone as far as possible under the present circumstances, but whatever the final decision we know that the deficiency we have produced can be relieved by epinephrine, and therefore epinephrine can act as an activator of the secretory system.

Dr. Korr has raised the question of the activation of epinephrine on other organs of the body. The only tissues we have studied besides the ciliary processes and the choroid plexus have been those of the kidney, and Dr. Flexner has not yet completed the studies on these. In addition, we have made some experiments on the frog's skin. This transfers water, and it is a favorite organ for the study of water transfer. The experiments revealed a difference in the redox potential between the epithelium and the corium of the skin in accordance with what one would expect from water transport. Beyond that we have not experimented on the skin.

There is one further point which I think is of physiologic interest. We have found that stroma of the ciliary body and also of the choroid plexus have no oxygen acceptors of their own. Respiration there can take place only through the oxygen acceptors of the epithelium. It is interesting to observe that at least half the cells of the stroma consist of capillary wall. If the metabolism of the capillaries in other organs of the body is similar to that of the ciliary body, then there is an interesting dependence of the respiration of the capillaries on the respiration of the surrounding tissues, involving a nonuse of oxygen by the capillary walls and the availability of oxygen to the surrounding tissues in amounts undiminished by its passage through the capillary walls. This would provide an available means through which the capillaries could respond to the oxygen needs of the tissues they supply.

SURGICAL CONSTRUCTION OF A LACRIMAL PASSAGE

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The following case is presented:

A white girl, aged 10, had had epiphora from the left eye since birth. This was so severe during winter months that it caused painful and disfiguring chafing of the left side of the face. Vision in this eye had always been poor, and the eye turned in.

The father of the girl also had esotropia, with amblyopia ex anopsia. None of the other relatives had congenital defects, and the family history otherwise did not contribute anything. The patient's own history was irrelevant with regard to the ocular disorders. She had developed mentally and physically better than the average child of her years.

Ocular examination revealed the right eye to have 20/20 vision. The lids, lacrimal apparatus, intraocular tension, conjunctiva, cornea, pupil, media and fundus were normal.

The left eye had only 20/70 vision with the best correction. There were 30 centrads of nonaccommodative comitant esotropia. Fusion was limited to intermittent simultaneous macular perception. The near point of convergence was 75 mm. The lids, intraocular tension, cornea, pupil, media and fundus were normal. Tears accumulated in the left eye and had to be constantly wiped away. The lacrimal gland appeared normal by inspection, palpation and function. No punctum was present in either the upper or the lower left eyelid. Examination of the nose revealed no obstruction or inflammation.

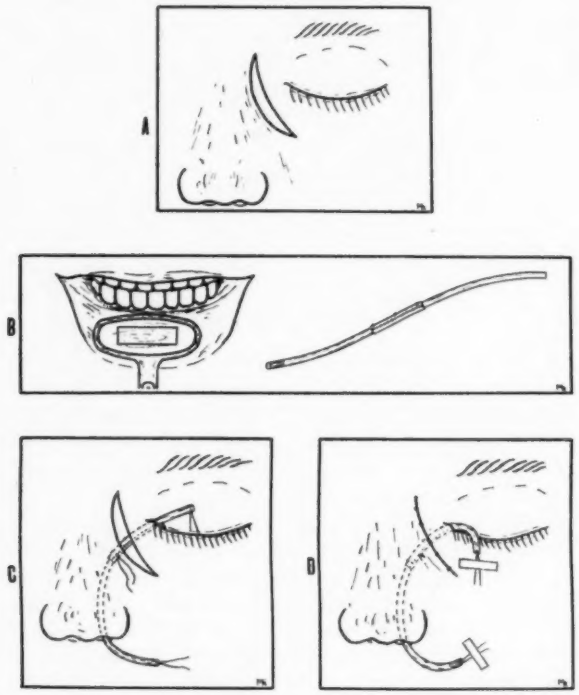
Opening the area of the lacrimal passage and probing had been advised. To carry out the instructions the left lacrimal fossa was exposed and explored on March 25, 1940. No lacrimal sac, canaliculus or other structure of the lacrimal passage apparatus was found. In the floor of the fossa an abnormal spur of bone about 4 by 4 by 2 mm. was present.

Since probing has been generally ineffective, it was decided to abandon that idea. Passages made of foreign materials have seldom been permanent and are often irritating; so other means were sought to try to overcome the troublesome epiphora by obtaining a passage for the tears.

It was reasoned that the closure of lacrimal passages appears to be due to the natural healing qualities of scar tissue, since it is a function of scar tissue to effect union of tissues. On the other hand, mucous membrane lines natural passages that remain open. Hence the logical step to take in constructing any passage intended to be permanent seems to be to attempt to line that passage with mucous membrane and to avoid

Read before the New York Academy of Medicine Dec. 15, 1941.

scar tissue. Conversely, to close a passage it might be reasonable to reverse this process and stimulate scar tissue and eliminate mucous membrane. With this idea in mind, a passage lined with epithelial tissue was made for the patient, and after two years this surgically constructed lacrimal canal, with openings in the conjunctival sac and in the nose, is 75 per cent as efficient as the normal passage of the right, the normal, eye and has shown no tendency to close. For two winters there has been no chafing of the face due to overflow of tears.



A, site of incision. *B*, mucous membrane from the mouth sutured on a rubber tube. *C*, the passage lined with mucous membrane. *D*, schematic appearance after completion of operation.

TECHNIC

With the patient under ether anesthesia the lacrimal fossa was explored through a crescentic incision about 18 mm. in length (*A* in the accompanying illustration). This was just nasal to the anterior lacrimal crest and was the incision usually made in doing a dacryocystorhinostomy. Careful search of the tissues revealed no evidence of canaliculi, lacrimal sac or canal. In the floor of the fossa there was the abnormal bone structure to which reference has already been made. The other structures were normal. An opening was made into the middle meatus from the lower portion of the lacrimal fossa after the anterior crest and the bone spur had been removed to secure a better operative field.

A 6 mm. hand trephine was used to start the opening and this was enlarged by means of a Kerison clamp. From the site where the lower puncta would naturally have been to this opening in the fossa to the middle meatus, a passage 3 mm. in diameter was made with a long narrow scalpel.

The lower lip of the mouth was clamped and everted, and an oblong portion of mucous membrane 20 by 30 mm. was dissected (*B*). This was fastened to a 2 mm. hollow rubber catheter by means of interrupted black silk sutures. The mucous membrane side was turned in to form the lining, and the dissected freshened side was turned out so that it might become engrafted to tissues of the new passage. The tube and the mucous membrane were then inserted into the passage and anchored in such a way that the graft lined the entire passage (*C*). One end of the tube extended out through the new opening nasally into the conjunctival sac near where the puncta should have been. The other end was pulled through the left nostril (*C* and *D*). Fixation was obtained by use of interrupted black silk sutures. A pressure dressing was applied for twenty-four hours and was replaced by a light dressing after the cornea had been examined for trauma. On the sixth day the anchoring sutures that held the rubber tube in place were taken out and the upper portion of the tube cut off. The remainder of the tube was then removed by being gently pulled down through the nose. The mucous membrane had apparently become adherent to the walls of the new passage. The sutures holding the edges of skin were removed at this time.

The new passage was found patent on the ninth day by irrigation. A 2 per cent solution of mercurochrome instilled in the conjunctival sac on the fifteenth day appeared in the nose in twelve minutes. A year and nine months after the operation the patient's father said the epiphora was only a tenth of what it had been before the operation. For the first time a winter had been passed without the child's face being chafed, and she was able to enjoy going out of doors in windy weather. Objectively, after two years at least 75 per cent function in the carrying of tears from the conjunctival sac to the nose appears to have been obtained.

SUMMARY AND CONCLUSION

It is unwise to generalize on 1 case, and a follow-up period of two years is short. However, it does appear rational to attempt to line with epithelium a lacrimal passage when permanent patency is the object.

40 East Sixty-Second Street.

FILARIA LOA REMOVED FROM UPPER LID

SANFORD R. GIFFORD, M.D.
AND
MICHAEL KONNÉ, M.D.
CHICAGO

From 1937 to 1940, one of us (M. K.) resided in Equatorial Africa as parasitologist and pathologist for the Belgian department of public health. The region was heavily infested with Filaria loa, 25 to 50 per cent of the native population showing at some time signs of infection.

In 1936 M. K. had shown an eosinophil count of 12 to 16 per cent, but examina- of the blood for microfilarias at that time gave negative results. In 1938 the first clinical signs of infection appeared, moderate swellings of the right arm which would last for six to twelve hours and disappear. In April 1940, when he was visiting Chicago on leave, pain about the left eye was felt and the parasite to be described could be seen moving beneath the lower part of the bulbar conjunctiva of this eye. M. K. consulted Dr. N. K. Lazar and was seen by one of us (S. R. G.) with him in consultation within two hours after the symptoms were noted. The parasite was still present and moving beneath the conjunctiva, raising a small ridge of the membrane over it in its rather rapid motions (fig. 1). It seemed to be from 2 to 2.5 cm. long, and one end was raised up repeatedly as if it was trying to escape through the membrane. The pain caused by these movements was not severe. There were no subconjunctival hemorrhages and only slight congestion. For various reasons, it was decided not to attempt removal of the worm at this time. Its movements under the conjunctiva ceased after eight hours. The next day a specimen of blood was examined by Dr. Opal Hepler, but no microfilaria were found.

On many occasions thereafter tender swellings were noted in various parts of the body, on the back, arms and chest. These subsided within several hours to two days. The worm never appeared again beneath the bulbar conjunctiva, but on May 2, 1942 movements could be felt beneath the right upper lid. A differential count on this day showed 20 per cent of eosinophils. When M. K. arrived at the office of S. R. G., the worm had again disappeared, but within an hour it reappeared and could be seen moving beneath the skin near the border of the lid. With the help of Dr. John Bellows, the needle of a syringe was passed beneath the worm, and a few minims of 4 per cent procaine hydrochloride was injected with the idea of paralyzing the worm. Immediately afterward a curved needle armed with silk was passed beneath the worm and out through the skin, and the loop of silk was drawn moderately tight about the fold of skin containing the worm. Swelling from the anesthetic and cessation of its motion made it impossible to see the worm, but an incision along the fold of skin revealed it. When grasped by a forceps, it

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moved with some vigor but was held by the loop of thread. When this was released, it was lifted out, apparently intact, one end adhering to the tissues but finally coming away.

The parasite was the size of a piece of surgical catgut and about 3 cm. long, with no definite head visible. Unfortunately it was first placed in a too concentrated solution of alcohol, which caused it to shrink, so that later attempts to unravel it for study resulted in a broken specimen (fig. 2). Preservation was sufficient, however, for identification of the worm as an adult female of the Filaria loa, the grasping parts at the anal orifice characteristic of the male being absent (M. K.; fig. 3). On the day after removal of the worm a pronounced swelling and redness of the lid were present, which cleared up in two days. Such

Fig. 1.—Appearance of the filaria under the bulbar conjunctiva.

swelling has been reported in other cases and is explained as due to freeing of toxic fluids from the worm during its removal. Swellings have since appeared in other locations, indicating presence of another parasite.

Cases of infection with filarias have rarely been reported in the United States. The only one we found in which the identical parasite was removed from the ocular adnexa was that of Landegger.[1] His patient had been a missionary in the Belgian Congo and had noted the characteristic calabar swellings eight years before. Three worms had been removed from the ocular adnexa in the Congo. When the patient was seen by Landegger, a worm was moving beneath the bulbar conjunctiva. Moving pictures of the worm's movements were made, after

1. Landegger, G. P.: Filaria Loa in Eye, Tr. Pacific Coast Oto-Ophth. Soc. **24**:230, 1939.

which it was easily removed through a conjunctival incision without any sort of fixation. Kilgore, of San Diego, Calif., in discussing Landegger's case described a similar one, the case also of a missionary from Africa, in which the worm was removed after fixation with a forceps through the conjunctiva. Jordan, on the same occasion, referred to a case in which he and Cooke, in Portland, removed a filaria from the anterior chamber of a patient who had never been away from the Pacific coast. The parasite could not be identified.

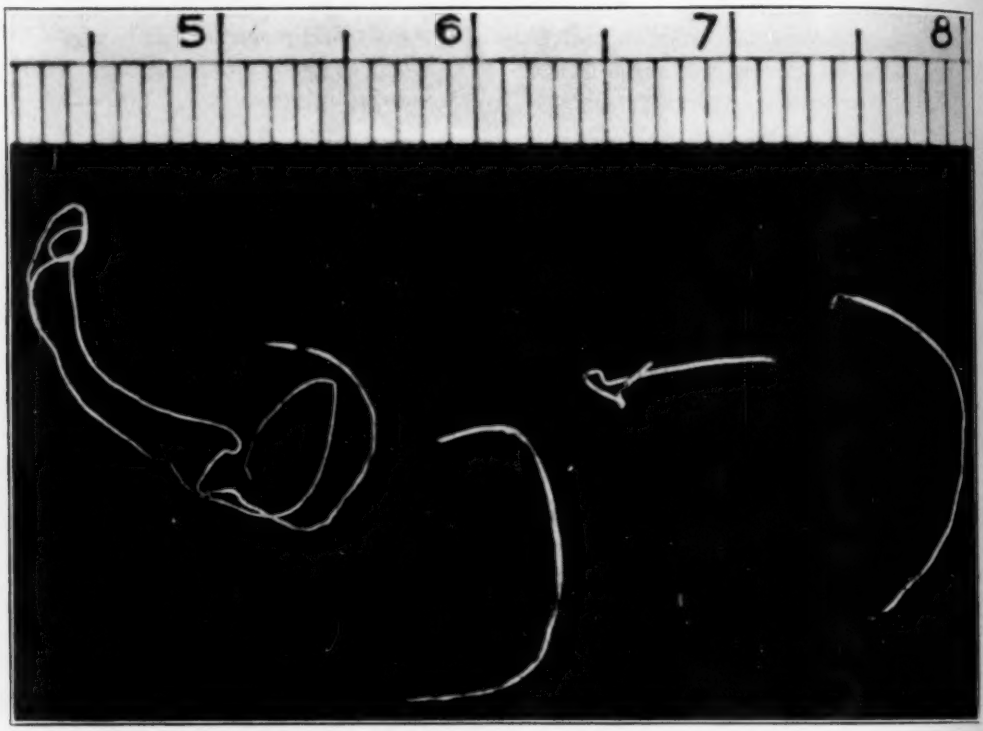

Fig. 2.—Fragments of the filaria after removal (about three times the actual size).

Stroschein [2] reported a case almost identical with the present one. The worm was held by a straight needle passed beneath it and removed through an incision in the skin without anesthesia. Elliot [3] referred to the frequency with which the worm appears beneath the conjunctiva and skin of the lid in natives of infested areas and described

2. Stroschein, E.: Filaria Loa am Auge, Klin. Monatsbl. f. Augenh. **102**:11, 1939.

3. Elliot, R. N.: Tropical Ophthalmology, London, Oxford University Press, 1920, p. 161.

use of a thread to prevent its escape during removal. Although it passes freely through the subcutaneous tissues all over the body, it is most frequently recovered from beneath the conjunctiva or skin of the lid because of the thinness of these structures. From this circumstance are derived various names for the parasite, such as "African eye worm," "Dracunculus oculi" and "filaria oculi humani." Its location in other areas produces the characteristic "calabar swellings," but, owing to the thickness of the skin, the worm itself is not often seen in these locations. Unlike the much larger guinea worm (Dracunculus medinensis), which perforates the skin for the purpose of laying its eggs and is commonly removed through one of its perforations, the adult of the genus Filaria loa never leaves its human host but has been known to live in it fifteen

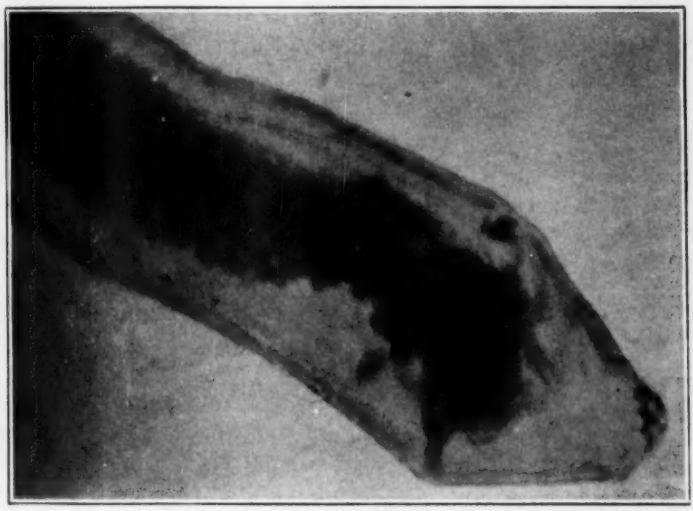

Fig. 3.—Posterior extremity of the filaria after removal (magnification approximately 40 diameters).

years or longer. Serious accidents referable to the worm have rarely been described. In one case of temporary hemiplegia the paralysis was ascribed to occlusion of a cerebral vessel, while in another case the worm was found in the pericardium at autopsy. Inoculation of the human host occurs through the bite of flies of the family Tabanidae (Chrysops dimidiata and Chrysops silacea). When larvae of both sexes are thus transmitted, as is usually the case, the human host becomes the breeding place of microfilaria. These appear in the blood stream only during the daytime, this characteristic being exactly opposite to the habits of Filaria bancrofti, which is found in the blood only at night. The occurrence of "calabar swellings" in any one who has inhabited an infested area suggests examination of the blood for microfilaria, which confirms

the diagnosis. In certain rare cases, such as the present one, only one viable worm or two worms of the same sex have been inoculated into the patient. In such cases no microfilaria are ever found in the blood stream and the worms eventually die without reproducing. Although numerous early cases of infection with Filaria loa were reported among Negro slaves imported into the West Indies and the United States, a proper vector was apparently absent, as the disease never became endemic and in all recent cases the patient has been at some time in Africa.

Another filaria which has been observed in the eye is Filaria bancrofti, common cause of elephantiasis in Asia. Its microfilarias have been seen in the anterior chamber by several observers, but the mature worms do not commonly appear under the conjunctiva or skin of the lids. The guinea worm, so common on the West coast of Africa, attains a length of 60 cm. and, as stated, penetrates the skin to lay its eggs outside the body. Onchocerca volvulus, a filariform nematode, has been well known in Central America as a cause of ocular lesions since the work of Pacheco Luna and recently of Quevedo.[4]

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4. Quevedo, A.: Ocular Onchocerciasis, Am. J. Ophth. **24**:1185, 1941.

CATARACT COMPLICATING CORNEAL SCARS AFTER PERFORATING ULCERS

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The present time will be memorable in the history of ophthalmology as the epoch of the invention of the slit lamp. However, this means of examining in vivo many different parts of the eye is not without its limitations. If one would learn how a lens fares under an opaque cornea one must have recourse to the older method of studying microscopic preparations. Not since the days of Wedl [1] and Becker [2] and later Treacher Collins [3] has there been made any important study of the microscopic pathology of the lens. The times require a descriptive and illustrated review of the subject to render more readily available the findings of the older workers, scattered in the literature, and, if possible, to add new points.

In a recent paper I [4] took as a theme a report on the primary changes in a lens that may occur during the active stage of a purulent ulcer of the cornea. My present endeavor is to follow up these changes to their ultimate results, months and years after the healing of the ulcer.

MATERIAL

Lenses from 36 globes with healed perforating ulcers of the cornea were studied. Only globes with perforating ulcers were included because in cases of healed nonperforating ulcers the indications are for removal of the cataract or for an operation to conceal the corneal scar rather than for an enucleation. Most of the eyes were lost because of a disfiguring staphyloma, secondary glaucoma or atrophy of the globe.

Age of Patients and Duration of Corneal Scars.—At the time of enucleation the age of the patient, when given, ranged from several months to 55 years. The period of existence of the corneal scar, when given, ranged from several months to fifty years.

Read before the American Ophthalmological Society, Hot Springs, Va., June 3, 1942.

1. Wedl, C.: Atlas der pathologischen Histologie des Auges, Leipzig, G. Wiegand, 1860-1861.

2. Becker, O.: Centralbl. f. prakt. Augenh. **6**:129, 1882.

3. Collins, E. T.: Tr. Ophth. Soc. U. Kingdom **12**:89, 1892.

4. Samuels, B.: Tr. Am. Ophth. Soc. **39**:66, 1941.

Causation of the Corneal Scars.—In most cases the scar was the result of a serpiginous ulcer. In the list there were several causes that are rarely encountered today, namely, scarlet fever, smallpox, ophthalmia neonatorum and measles.

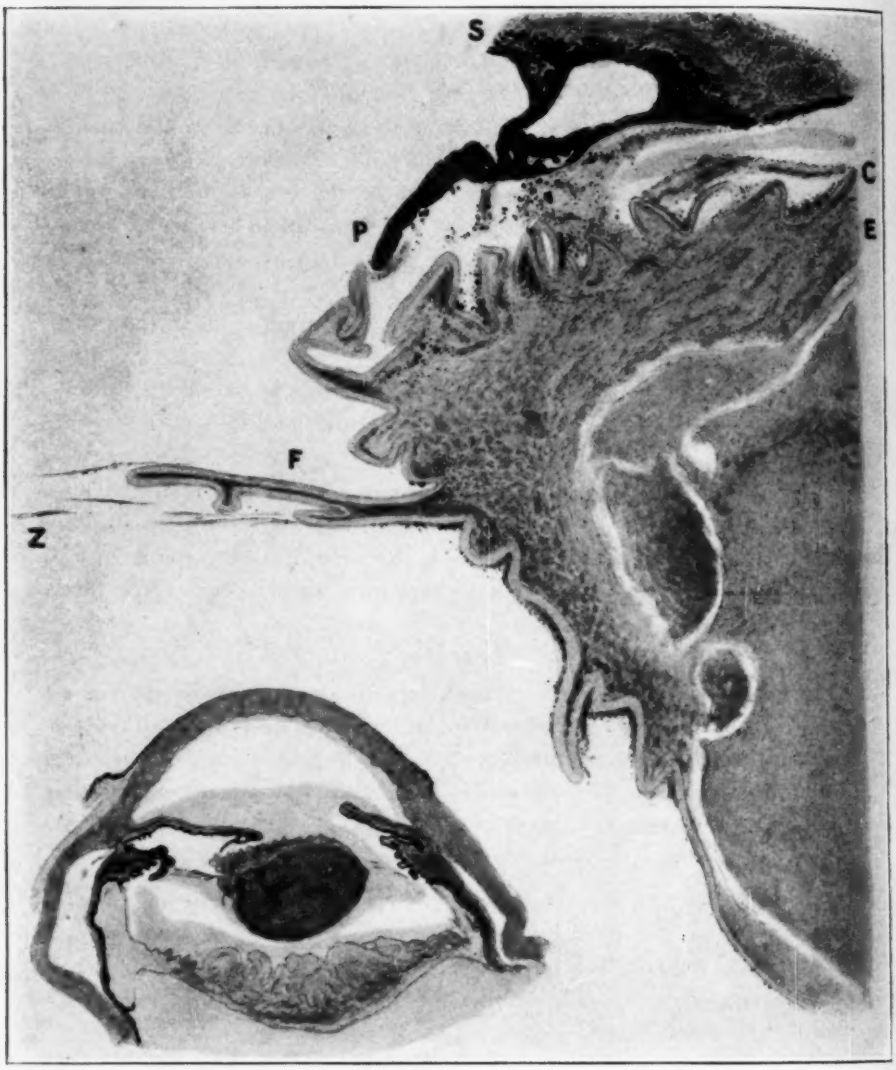

Figure 1

(See legends on opposite page)

PATHOLOGIC OBSERVATIONS

General State of Lenses and Effects of Traction.—As a result of widespread corneal ulcers the lenses were severely damaged. Ten were transformed into a membranous cataract. Seven were adherent to the

cornea. In 23 the capsule was found to be intact. It makes a difference in the study of a cataract whether or not the capsule has been opened. If the opening is large enough, mesodermic tissue may enter and transform the lens into a membranous cataract. A number of lenses were adherent to the corneal scar. On the other hand, occasionally an enormous space separated the lens from the cornea, especially when there was a globular staphyloma (figs. 1 and 2). Most lenses were more or less shrunken and disfigured, but several were swollen. In several cases of globular staphyloma of the cornea and ectasia of the remainder of the globe the lens was flattened, owing to traction exerted by way of the zonular fibers as a result of an increase in the circumference of the ciliary body.

In connection with the increased width of the circumlental space accompanying globular staphyloma of the cornea, there came to mind a physiologic detail that should be remembered in the manipulation of an intracapsular extraction. If the theory of von Pflugk, of Dresden,[5] which has met with great opposition, is true, that the lens capsule is less elastic than the zonular fibers, then in the 5 buphthalmic globes studied the zonular fibers should have been elongated and the ciliary processes drawn inward toward the lens. On the contrary, it was always the lens capsule that yielded and was pulled outward by the zonular fibers (fig. 1). In the enlarged eyes the lens, far removed from the staphylomatous cornea and the ectatic scleral spur, appeared singularly isolated and dwarfed. A flattened anterior capsule and a decidedly bulging posterior capsule characterized its shape. When traction is made at the equator the posterior capsule, being thinner and less resistant than

5. von Pflugk, A.: Arch. f. Ophth. **128**:179, 1932.

EXPLANATION OF FIGURE 1

The eye of a 19 year old girl. An ulcer perforated at the lower margin of the cornea (not shown).

In the small picture the anterior chamber is seen to be deep, but the filtration angle is blocked. To the right a new-formed membrane on the iris has caused an ectropion of the uvea. To the left the pupillary border is adherent to the shrunken lens. The anterior capsule is thrown into numerous folds. The underlying cataract extends to the equator on the left side, where a fold of the capsule is drawn out into a strand. The flat part of the ciliary body is covered by a membrane. The retina is detached and is intricately folded from one ora serrata to the other.

The large picture shows the left equatorial region of the lens. The capsular epithelium (*E*) has formed a thick layer anteriorly, extending backward to the equator (equatorial subcapsular cataract). Some folds of the capsule are exceedingly elongated. The spaces embraced within the bases of the folds are filled out by proliferated epithelium. An especially long fold (*F*) is the result of traction by zonular fibers (*Z*). The iris with its sphincter (*S*) is made adherent to the lens by means of a membrane. The pigment epithelium (*P*) is drawn out by traction.

the anterior, is pushed backward by the lens substance, whereas the thicker and more resistant anterior capsule is leveled (fig. 3, small drawing).

In 9 lenses the cortical substance seemed to be entirely fluid. Histologically, it is not easy to decide whether or not an area is fluid, because solid lens matter often appears to be as homogeneous as coagulated albuminous fluid. In favor of the fluidity of a lens are the following points: first, a perfectly homogeneous zone surrounding the nucleus and sharply outlined against it; second, minute, shadow-like, empty globules lying in a perfectly uniform medium and adhering to masses that are evidently not fluid, and, third, a granular appearance of the entire lens substance so that neither lamellas nor other details

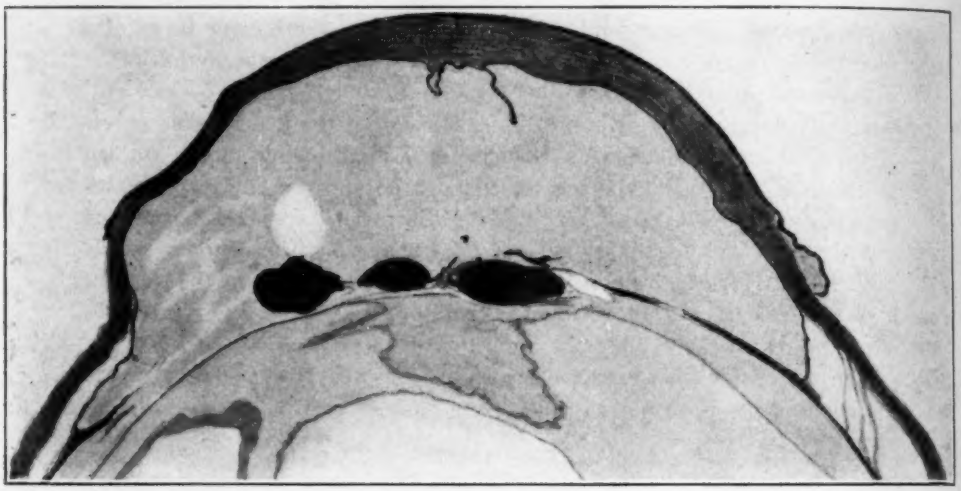

Fig. 2.—The anterior zone of a buphthalmic globe. To the left is an intercalary staphyloma. The anterior chamber is entirely abolished. Of the lens three separate oval masses remain. Originally the lens was attached to the iris and the cornea by synechias, of which there is still some pigment adhering to the lens and filaments of pigment extending backward from the staphyloma. The ciliary processes are drawn out into mere strands, especially on the right side.

can be recognized. Under the last circumstance it would be assumed that the lens became cataractous at an early age, before enough time had elapsed for a solid nucleus to form.

Morgagnian Cataract.—Three lenses with morgagnian cataracts were observed, in each of which, owing to the fluidity of the cortex, the solid nucleus had changed its normal position. Occasionally in children's eyes the embryologic nucleus of Vogt appears under the microscope to have a decidedly solid consistency. This was demonstrated in the eye of a 17 year old girl who was blinded in this eye by a perforating

ulcer twelve years previous to enucleation. The nucleus was so large that it was recorded as "gigantic." It was identified by its distinctly grayish color, sharp outline and globular shape. When in a child's eye such a swollen lens is needled it is possible for the nucleus to be dislocated into the anterior chamber, where it appears clinically as a yellowish sharply outlined mass.

Calcification of Lens.—Notwithstanding that these were all complicated cataracts and that many were of long duration, yet only 4 lenses showed extensive calcareous degeneration. The impregnation took

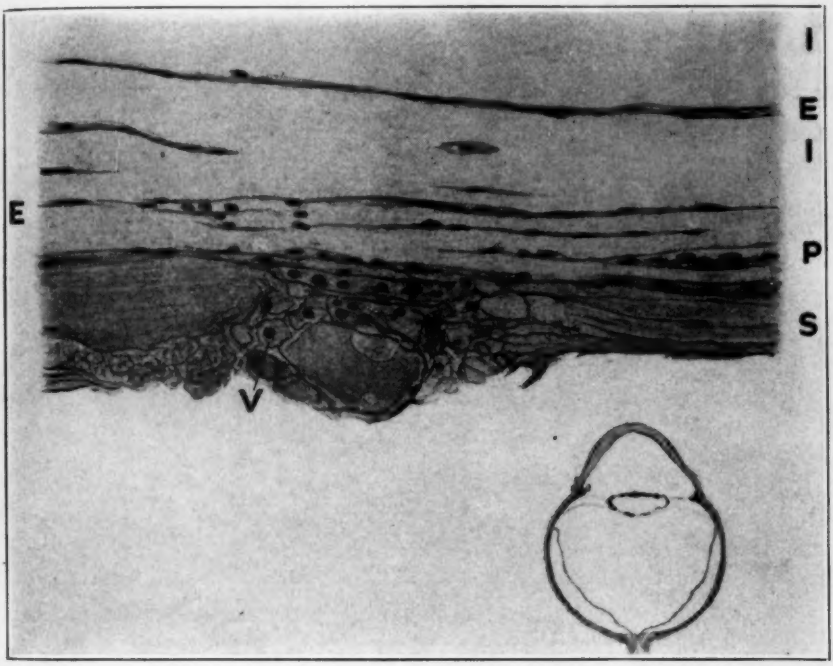

Fig. 3.—The eye of an 8 year old boy. Following a perforating ulcer of the cornea, a staphyloma developed, as is indicated in the small drawing. A small pyramidal cataract developed. The large drawing is a detail of the posterior part (*P*) of the cataract at its border on the lens substance (*S*). Traversing the almost homogeneous substance of the capsular cataract (*I*) are files of epithelium (*E*). On the posterior surface of the cataract the epithelium has proliferated and formed vesicular cells (*V*), which are partially surrounded by debris of lens matter.

place in the anterior and equatorial cortical substance in the form of an inverted shallow saucer. Why this site was chosen could not be explained, although it was recalled that the irritating substances came from in front.

In 1 case there was a deposit of chalk within the solid substances of an anterior polar cataract (fig. 4). This is unusual, because the preferential site of chalk is in liquefied parts of a lens. In a very shrunken cataract a small amount of hyalin was found, and in another there were numerous slitlike spaces left by dissolved cholesterol crystals (fig. 5).

Ossification of Lens (So-Called).—In a globe that had become atrophic after a perforating eczematous ulcer, vascular connective tissue, chalk and bone were encountered within the lens capsule (fig. 6). The explanation of the presence of bone in this organ of purely epithelial origin lay in the fact that the adjacent connective tissue, itself partly converted into bone, through some opening in the capsule must

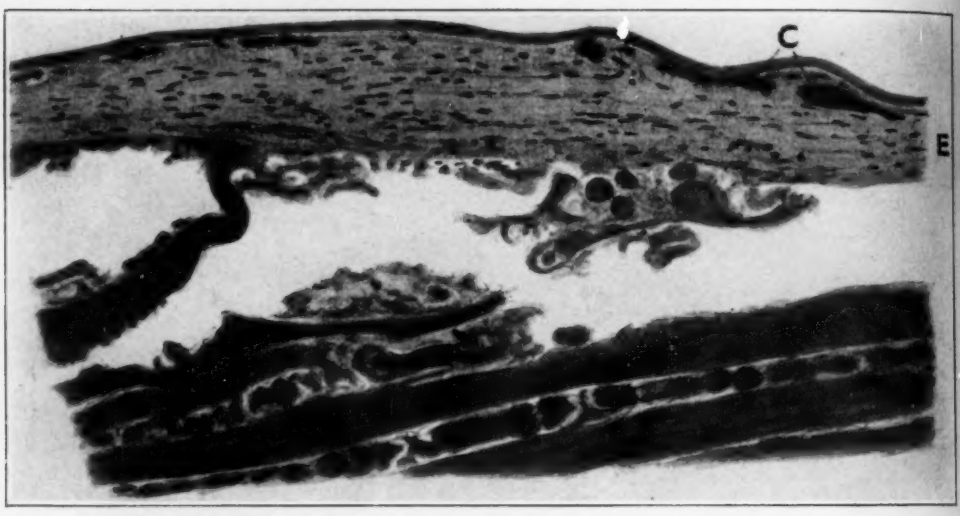

Fig. 4.—In a case of staphyloma of the cornea the capsular epithelium proliferated to a remarkable degree (*E*). At *C* there is an unusual occurrence in an anterior capsular cataract, namely, a deposit of chalk. Many morgagnian globules are present in the disintegrated lens substance.

have entered and formed the basis of the intracapsular bone. Calcareous degeneration is not uncommon in old cataractous lenses, but it is an axiom that before bone can be formed within a lens capsule, connective tissue must first have been introduced.

Spontaneous Expulsion of Lens.—A small disfigured calcified lens was caught in the act of perforating the globe (figs. 7 and 8). A sharp angle of the lens, preceded by a sliver of chalk, pointed into the loose tissue of a corneal scar. The surface epithelium was hydropic and on the point of disappearing. The lens stood ready to escape as soon as the sliver of chalk had been thrust off. Spontaneous extrusion of a

lens, acting as an intraocular foreign body, has been described a few times. The process of extrusion is dangerous with regard to late infection, because germs readily penetrate along the path of the escaping lens and enter directly into the vitreous, causing endophthalmitis septica (fig. 5).

Changes in Lens After Rents in Capsule.—A number of times an hourglass-shaped formation, known as Soemmering's crystalline swelling, was encountered (figs. 2, 9 and 10). This is a common but always interesting feature of secondary cataract in which the nucleus has been

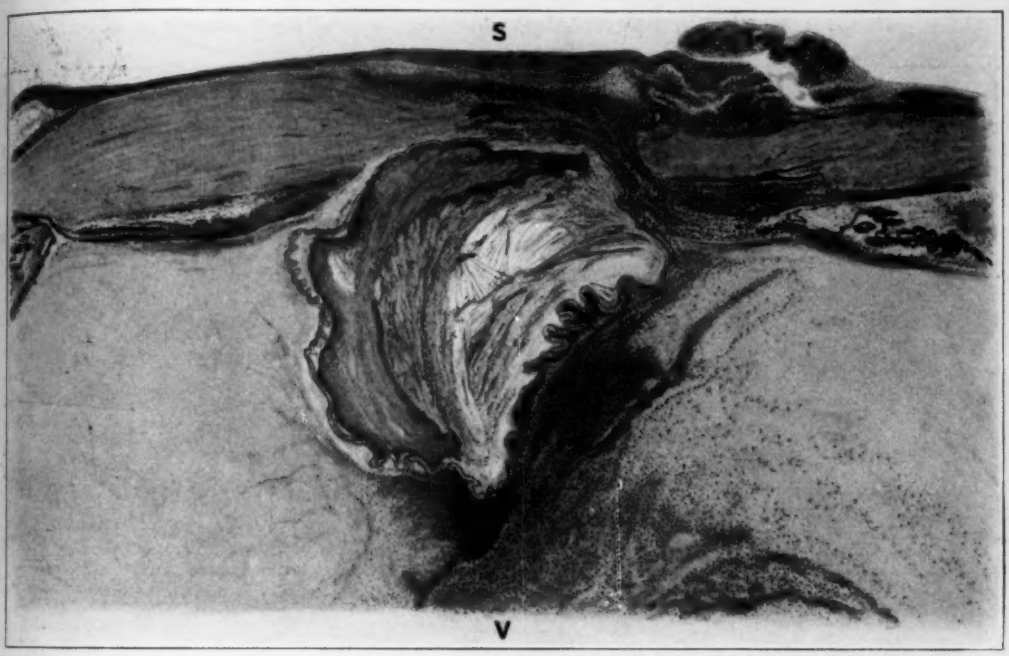

Fig. 5.—Seventeen years prior to enucleation a serpiginous ulcer perforated, leaving a leucoma adherens. Recently the eye had become inflamed. In the drawing all that remains of the cornea is shown to the left. A densely infiltrated scar (*S*) containing blood vessels and free blood is in the center. The iris is pressed against the cornea, and in the pupillary area the shrunken lens is adherent to the scar. Anteriorly and to the right the lens is surrounded by pus. The lens capsule is ruffled. Apparently the lens is tilted so that the equator is now in the long axis of the eye. The layers of the lens to the left, corresponding to the anterior surface, are calcified, and in the posterior layers there are many spaces left by cholesterol crystals. The cells within the lens are pus cells which must have entered through a defect in the capsule. The epithelial cells have entirely disappeared. To the left the slitlike extension of the pigment represents the path of an operative wound. The ciliary body is lined with pus, and in the vitreous (*V*) is an abscess. In this case the incarceration of a calcareous lens led to a breaking down of the leukoma and to late infection. Germs entered the eye and immediately reached the vitreous, producing an abscess.

expressed through a central opening in the anterior capsule. Generally, when the lens is not extracted in its capsule the germinal layers at the equator remain. Lacking the support of the nucleus, the anterior capsule folds on itself and falls back to be applied to the posterior capsule, enclosing and protecting the germinal cells from the destructive action of the aqueous. The cells continue to proliferate and to produce transparent but abortive fibers. A tautly distended cushion on each side of the central membrane is characteristic of the youthful eye, being an expression of the active regenerating power of the cells. In the aged the ring is apt to be oval, the proliferation of the cells being too sluggish to distend the capsular wall (fig. 9). In performing a dis-

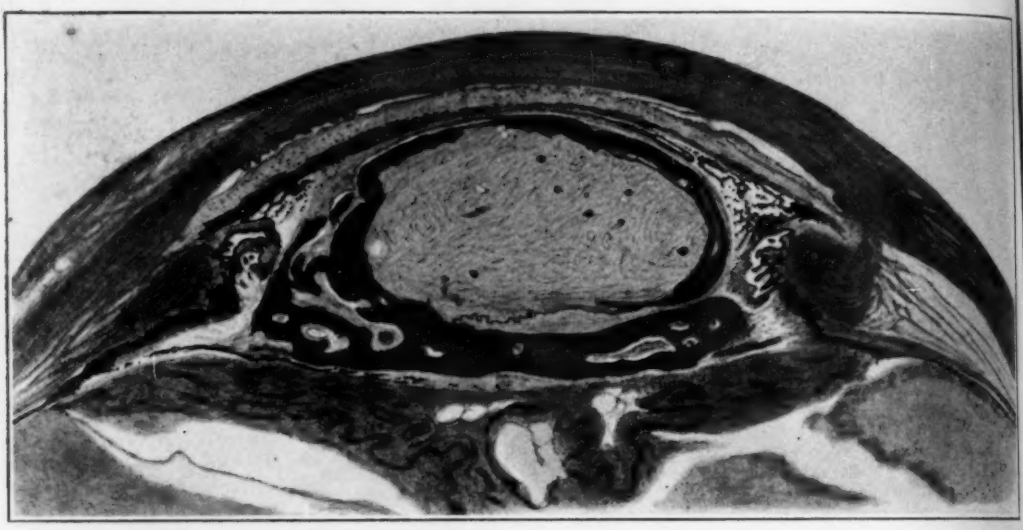

Fig. 6.—The eye of a 16 year old boy. As a result of a perforating eczematous ulcer a leucoma adherens developed (not shown). The section is faintly stained as a result of decalcifying of the lens. The iris is pressed against the cornea. A membrane containing large trabeculae of bone anchors the lens to the ciliary body and presses it against the cornea. The posterior lens capsule is crinkled. Anteriorly and on the right the subcapsular layers are calcified. The interior of the lens substance is replaced by an ingrowth of the neighboring connective tissue. The bone that embraces the lens posteriorly and on the left shows many lacunas containing bone marrow and blood vessels. The retina is totally gliosed. The epithelium of the lens has entirely disappeared.

cission on a secondary cataract, one is surprised at how much lens matter may be extruded from an opening in Soemmering's crystalline ring.

Effects of Glaucoma.—Twenty-three of the globes were glaucomatous. Glaucoma seemed to have played a double role in the removal of these eyes. In the first place, increased intraocular pressure probably

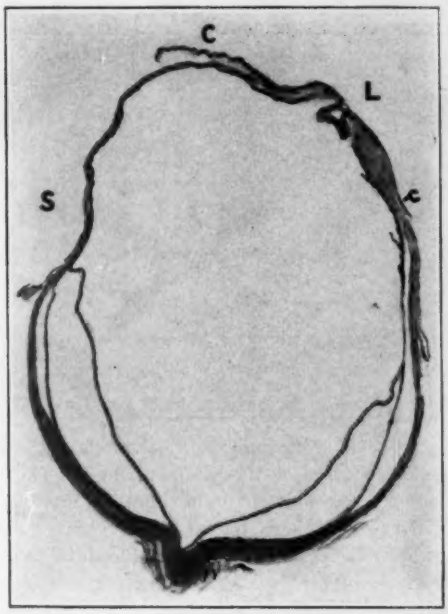

Fig. 7.—The eye of a 17 year old girl. The eye was injured four days after birth and was operated on two years later. The conjunctiva (*Cc*) indicates the site once occupied by the cornea, which is here replaced by a staphyloma. The scleral spur was originally at *S*. The thin tissue between *C* and *S* is a large intercalary staphyloma. The retina is artificially detached. The optic nerve shows a glaucomatous excavation. The iris and ciliary body have almost disappeared. The lens (*L*) is transformed into a shrunken mass. This is adherent to the staphyloma in the pupillary area, as is indicated by an absence of epithelium.

Fig. 8.—Detail of figure 7. The disfigured and calcareous lens is incarcerated in the staphyloma (*St*). The vitreous (*V*) surrounds the lens and is adherent to the staphyloma. Anterior to the lens a sliver of chalk is embedded in the staphyloma, lying almost in contact with the edematous and cystic epithelium (*E*). At *P* is a lining of pigment epithelium.

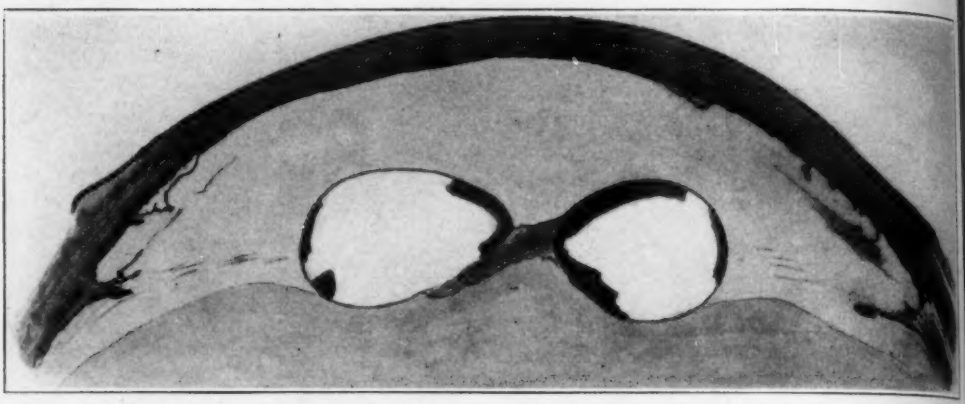

Fig. 9.—The eye of a 14 year old child. Ten years before enucleation an ulcer of the cornea developed as a result of smallpox. The cornea is replaced by a staphyloma lined by the pigment epithelium of the iris. The wide space between lens and ciliary body indicates to what great extent the globe was enlarged. The central area of the lens is replaced by a dense fibrous band bridging over a crystalline ring of Soemmering. In cross section the whole formation presents the outlines of an hourglass. The processes to the right are put on the stretch, owing partly to the enlargement of the globe and partly to the shrinkage of the lens.

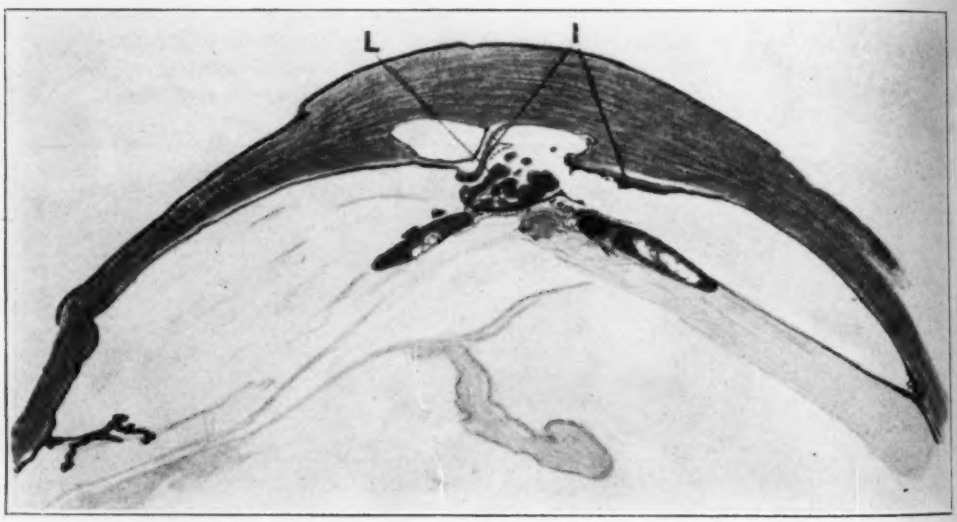

Fig. 10.—Staphyloma of the cornea. The membranous lens, being adherent to the iris, is drawn forward, taking with it the vitreous. Remnants of the iris (*I*) are still visible on the posterior surface of the staphyloma. Anterior to a layer of pigment that is glued to the membranous cataract, loose lens matter (*L*) is to be seen. The ciliary processes are exceedingly attenuated and put on the stretch.

was one factor in producing the cataracts, as is the case in primary glaucoma, and, in the second place, glaucomatous symptoms, as already noted, led to the removal of some eyes. Usually in a glaucomatous eye the lens is swollen and its capsule distended and without folds. So it was in the lenses of 13 of the glaucomatous globes, but in 10 the lens was shrunken from causes other than glaucoma.

Separation and Folding of Capsule.—Folds and separations of the capsule from the lens substance were outstanding features in many of

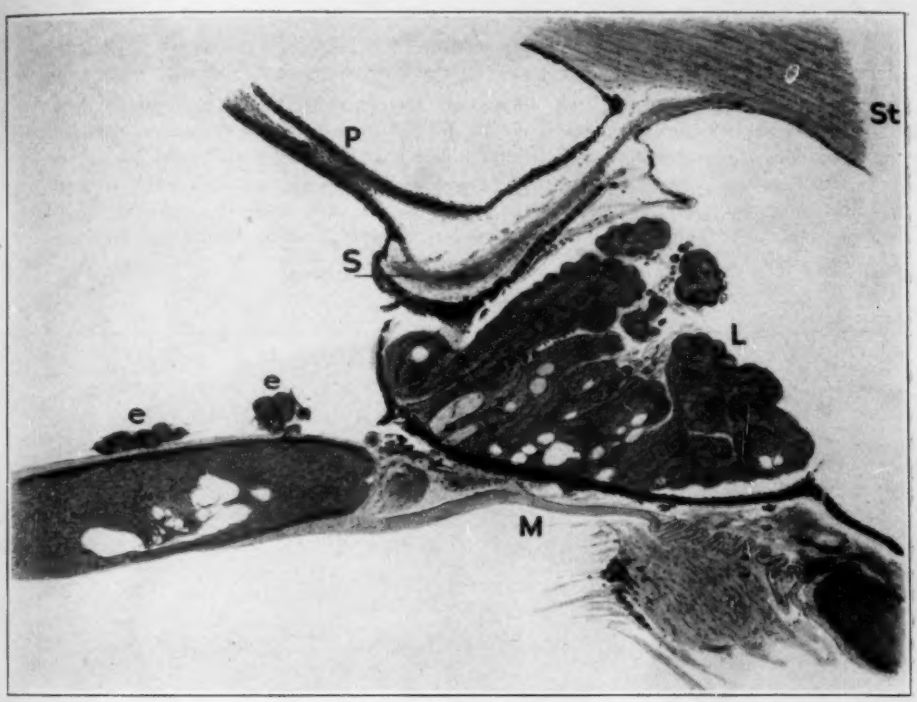

Fig. 11.—Detail of the central area of figure 10. Portions of the sphincter muscle (*S*) of the pigment epithelium (*P*) of the iris cling to the posterior surface of the staphyloma (*St*). Masses of free lens matter (*e, e*) lie directly on the surface of one roll of a Soemmering crystalline ring. They all consist mostly of vesicular cells. A large group of the same type of cells (*L*) has proliferated between the sphincter (*S*) and the membranous cataract (*M*), which is covered by a pigmented layer.

the lenses. As a rule they were confined to the anterior capsule, being rarely seen at the equator and posterior pole (figs. 4, 12, 13 and 14). The largest folds and detachments appeared in the lenses that showed the greatest shrinkage of the lens substance. In some instances they were the results of an anterior capsular cataract that interposed itself between the capsule and the lens substance. As the capsule is adherent

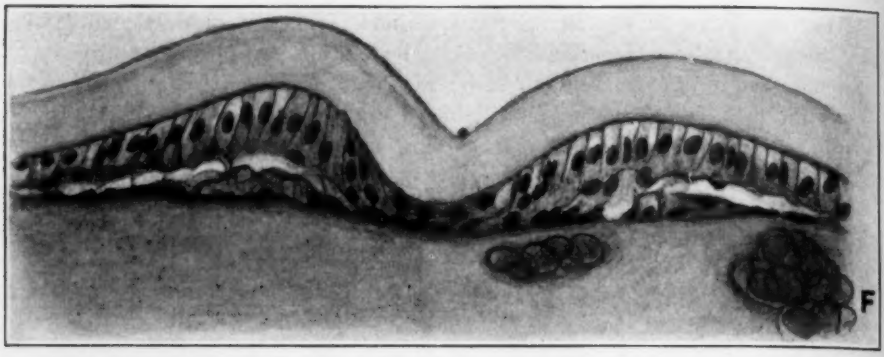

Fig. 12.—The cornea (not shown) is transformed into a total staphyloma. The lens is completely cataractous. In the pupillary area the capsule is detached from the lens substance and thrown into folds. The epithelial cells lining the elevations are elongated and have assumed a palisade arrangement. Beneath the layer cells, with nuclei at right angles to the surface, there is another layer of cells, of irregular contour, with nuclei parallel to the surface. Cataractous lens matter is at *F*.

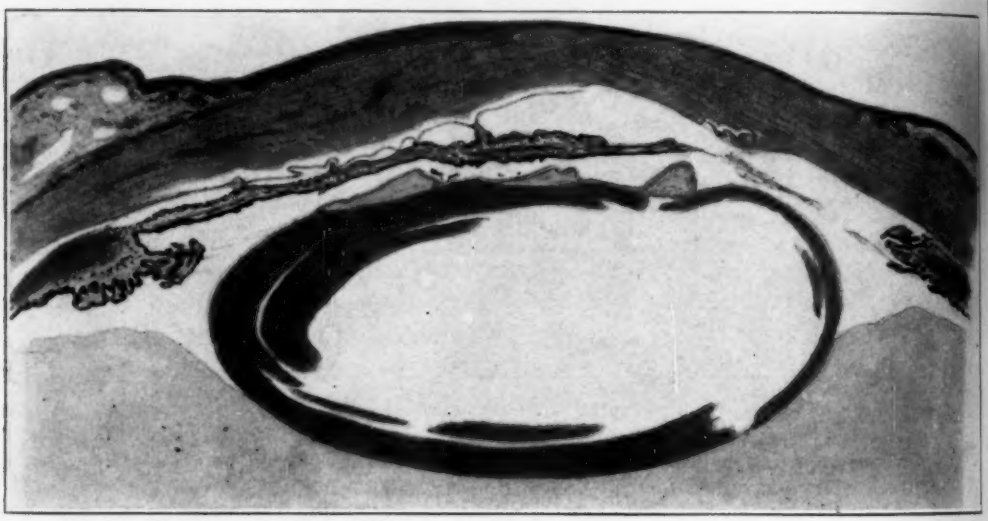

Fig. 13.—A year before the enucleation an ulcer of the cornea developed and perforated, as a result of lagophthalmos. A prolapse of the iris was excised. In the picture the detachment of Descemet's membrane is an artefact. Its disappearance in corneal tissue to the right marks the place of excision of the iris. To the left the cornea is replaced by a leukoma containing new-formed blood vessels enveloped by plasma cells. The iris that remains is attenuated. The anterior capsule of the lens shows three separate pyramidal-shaped elevations, each caused by an anterior polar cataract. A layer of epithelial cells lines the base of each one. The cataract consists of hyalinized tissue showing a few elongated cellular elements.

to the dense tissue of a subcapsular cataract, when the latter contracts, the capsule, not being elastic enough to follow, is thrown into folds. The capsule may also be folded by the contraction of a membrane on its anterior surface. In 1 instance, corresponding to the cataract, the folds embraced a diameter of 6 mm., an expanse larger than that of the pupillary area (fig. 14). An unusual feature was seen in a case in which the capsule beneath the iris showed three abrupt and separate pyramidal elevations (fig. 12).

Proliferation of Subcapsular Epithelium.—Each proliferation of the subcapsular epithelium encountered was considered primarily to have been started by the stimulating effect of toxins emanating from a corneal

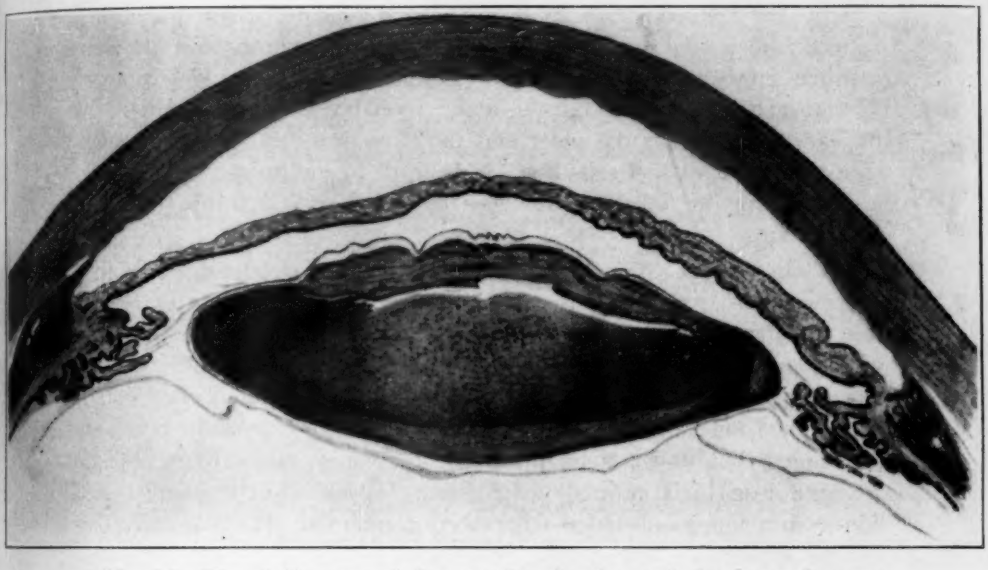

Fig. 14.—The shallowness of the anterior chamber and the forward curvatures of the iris indicate that a leucoma adherens existed (not shown). The lens is *in situ*. Almost the entire anterior capsule is detached from the lens substance by a thick layer of almost homogeneous tissue laid down by the capsular epithelium. The slit that separates the cataract from the lens substance is an artefact indicating poor adhesion in life. The lens substance is completely cataractous. To the right at the equator there is a large vacuole in the germinal layers. The ciliary body and the vitreous appear to be normal.

ulcer. No doubt in some instances trauma, incidental to the perforation of the ulcer and to the loss of the chamber, was a factor. The idea that toxins were the chief cause of the cataracts was based on the fact that the changes in the lenses were confined chiefly to the pupillary area, which is not protected by the iris. However, the finding of three discrete pyramidal cataracts under the iris and beyond the exposed

area gave the impression that in this particular case the cataracts were the result not so much of a weakened stimulus as of a strong inclination on the part of the cells to multiply (fig. 13). The inherent capacity of epithelial cells to grow is convincingly demonstrated by their behavior in culture mediums. Once started, an anterior capsular cataract, it would seem, continues to grow, like the circumscribed thickening of the skin of a callus, long after the exciting cause has been removed.

In 1 case a dense band of connective tissue extended between the staphylomatous cornea and the lens. In the area of the lens covered by the band the epithelium was without any visible change, but in the uncovered area the epithelium had produced a pyramidal cataract. It was believed that here toxins from the corneal ulcer produced two effects: the appearance of an inflammatory exudate, which was transformed into a connective tissue band, and a multiplication of the subcapsular epithelium, which was transformed into a pyramidal cataract. The exudate, although of itself toxic, probably was less so than the primary toxins from the ulcer and therefore was not virulent enough to excite the epithelial cells that lay beneath to multiply.

According to Salzmann the lens epithelial cells fall into two biologic groups:

1. The central group, which is confined to the pupillary area and a narrow zone surrounding it. It comprises a layer of cells extremely thin and transparent which forms an organic union between the body of the lens and its capsule. It is by the action of these cells that the fibrous part of the lens is said to be nourished. Under normal conditions the anterior subcapsular epithelial cells remain relatively unchanged, but under toxic influences they may undergo metaplastic changes, lose their normal cubic form, become spindle shaped and lay down a tough substance—the anterior cataract. Histologically this has the appearance and staining reaction of connective tissue, for which it may be mistaken. However, it retains the chemical reaction of epithelium (figs. 3, 4, 13 and 14).

2. The equatorial group, which forms the true germinal zone of the lens. Throughout life the germinal cells retain their original capacity to produce fibers, so that the lens substance is being continually augmented. Under abnormal stimuli they may produce a vesicular type of cell, very different from the spindle-shaped type produced by the cells at the anterior pole (fig. 11).

In this survey, when it came to metaplasia a strict line of demarcation between the two biologically different groups of epithelial cells could not always be drawn. Occasionally vesicular cells were produced by the anterior subcapsular epithelial cells (fig. 3) and, analogously, but more rarely, spindle-shaped cells by the germinal cells (fig. 1).

Most of the anterior subcapsular cataracts were far advanced, and yet no matter how extensive their breadth their thickness never went beyond a certain limit and never encroached on the nucleus (fig. 14). Time is required for this formation to develop, and therefore in the active stage of a purulent corneal ulcer it is seldom found.

From the earliest times anterior cataract, both congenital and acquired, on account of its singular form and position, has been a favorite subject of study. The acquired form was observed clinically and reported accurately by von Arlt [6] in 1885. He explained that the taut band that sometimes surmounts an anterior polar cataract is but a remnant of an exudate that plastered the lens to the cornea during the period when the chamber was lost after the perforation. As the ulcer heals and the cornea is pressed forward by the aqueous the exudate, which remains adherent to both cornea and lens, is slowly extended into a band or mere thread (fig. 2).

In a few lenses, instead of proliferating in the shape of spindle cells, the subcapsular epithelial cells merely showed distortion or disorder (fig. 12). Occasionally the epithelial cells were missing over stretches where the cortex had undergone liquefaction as a sign of the highest degree of faulty metabolism.

Posterior Spread of Anterior Subcapsular Epithelium: In a number of lenses in which the normal whorl-like arrangement of the germinal cells at the equator had been disturbed the anterior cells crept along the equator and beyond it until the entire posterior capsule was lined by them. In this way the two poles were brought to resemble each other, the distinction being made by a difference in the thickness of the two capsules, the posterior being thinner than the anterior.

Correlation of Clinical and Pathologic Observations.—It is not an uncommon clinical experience to be misled as to the consistency of a lens by its color. Clinically a lens is supposed to be hard and calcified when it is shrunken, has an uneven surface and a very white color. One lens described in its history as being calcareous proved to contain no chalk, to be semifluid and to be filled with pus cells from an injury.

Vesicular Cells.—A vesicular cell is a peculiar-appearing swollen spherical or polygonal cell of large size, having a well defined border and a large faintly staining nucleus. As it is primarily a product of a germinal cell its field is at the equator. Treacher Collins [8] attributed the formation of vesicular cells to diminished intracapsular pressure caused by degeneration and shrinkage of the lens substance. Several times in the specimens it was noted that, although the germinal zone

6. von Arlt, C. F.: Clinical Studies on Diseases of the Eye, translated by L. Ware, Philadelphia, P. Blakiston, Son & Co., 1885.

was in great disorder, no vesicular cells had formed, as if the cells did not possess enough vigor to produce even abortive lens fibers.

An endeavor was made to ascertain whether there was a relation between vesicular cells and changes in the vitreous body. No evidence was found that membranes in the vitreous exerted any influence on their existence. It was borne in mind that the presence of vesicular cells represents but a temporary state in the long run of cataract formation and transformation. It is their fate, as the cataract becomes older and more fluid, to grow paler, burst and disappear. In a morgagnian cataract they are not to be found in quantity because they seem to require at least a certain amount of colloidal resistance for their development.

Extracapsular Proliferation of Epithelium.—A most informative specimen came from a staphylomatous globe with a cataracta accreta (figs. 10 and 11). There was no history, but the nature of the staphylomatous cornea and the stretched appearance of the ciliary body left no doubt that the corneal scar was many years old. Of the lens there remained on each side a ring of Soemmering connected by a membrane. Within the ring there was an abundant proliferation of capsular and vesicular cells. As a result of disintegration of some of the vesicular cells, multilocular spaces had developed, which were filled with a faintly staining fluid.

Anterior to one ring there were two small groups of epithelial cells which were certainly not within a capsule but were perhaps protected by an albuminous film of their own, as was suggested by a faintly staining zone that surrounded them. A conglomeration of similar cells lay in the pupillary area in the embrace of a pigmented layer that lined the posterior surface of the sphincter muscle and extended back to line the membrane that connected the rings. The extracapsular structures were all diagnosed as lenticular cells because of their intense staining reaction, their compactness, their sharp outlines and their resemblance to the cells and spaces within the rings. In nearly every cell there was a nucleus, which gave additional evidence of their lenticular origin. It was believed that the possession of so many nuclei and the compact arrangement of the cells were factors that helped to preserve them in a fluid medium.

This special case assumed importance for two reasons: first, because lens epithelium had proliferated outside of the lens capsule and entirely independent of it, and, second, because groups of living epithelial cells had maintained themselves, perhaps for years, free in a chamber filled with fluid.

It would have been easy to explain the presence of the masses by taking for granted that they were cells that had escaped from the lens at the time the capsule ruptured. However, they were evidently fresh cells which seemed to be making an attempt, although abortive, to create

a new lens to take the place of the one lost. It is known that if an eyeball is removed from the fetus of a salamander and particles of lens are taken from it and introduced under its skin they make no effort to form a lens. It is not until particles of embryonic retina are introduced with the lens that a new lens is produced. Perhaps in the present case an attempt to form a new lens came about through a similar coincidence between the originally extruded epithelial cells and some constituent of the fluid in a cavity largely lined by pigmented epithelial cells.

The microscopic observation of extracapsular masses of epithelial cells served to explain what the pearls and globules are that sometimes appear in the prolapsed vitreous after a discission has been made in a secondary membrane. These formations have a permanency about them, and it is likely that they are small groups of lens epithelial cells that have developed into miniature lenses. Possibly, when clumps of epithelial cells are isolated in the stroma of the vitreous they are better able to preserve themselves than when wafted about in the aqueous.

Cowan and McDonald [7] gave a clinical description of a large conglomerate transparent mass resting on the anterior surface of the iris after an extracapsular extraction. They surmised that it was composed of globules of transformed lenticular bladder cells. Elschnig [8] observed such cells clinically and identified them under the microscope as vesicular cells—hence the term "Elschnig's pearls." He explained that they are most apt to be found after an extracapsular extraction in which an especially large portion of the anterior capsule has been excised. This procedure makes it difficult for the narrow rim that is left of the anterior capsule to fold and fall back completely onto the posterior capsule. Through crevices thus left epithelial cells may escape and proliferate in the aqueous.

Dead Lenses.—In spite of the fact that so many of the 36 lenses studied had been diseased over a long period of years, with the exception of 4 they all showed living epithelial cells. These 4 were recorded as "dead lenses" in the strict sense.

57 West Fifty-Seventh Street.

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ALLERGIC KERATOCONJUNCTIVITIS

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On rare occasions during the past five or six years an unusual type of corneal lesion has been seen in association with dermatitis of the eyelids and conjunctivitis. Suspicions were entertained that these conditions were allergic, but only recently has it been proved that they are due to contact with certain specific agents, such as drugs, cosmetics, foods and bacterial toxins.

Reference to the literature revealed relatively few reports of allergic keratoconjunctivitis. Among them were reports of keratitis parenchymatosa with urticaria, by Stern [1]; of peculiar subepithelial infiltrates which appeared after ingestion of antipyrine, by Sjögren [2]; corneal ulcers due to allergy to orris, by Parlato [3]; superficial keratitis with pollen allergy, by Manksch,[4] and corneal destruction by contact with procaine hydrochloride and pontocaine hydrochloride, by Klar.[5]

Hypersensitivity of the tissues to certain specific agents is seen most frequently in the skin and mucous membranes; however, it may occur in other structures. Having been sensitized to an agent, the tissues react to contact with this allergen in an unusual and abnormal manner, i. e., with an inflammation. The reaction may be rapid in onset and transitory in nature, or it may develop slowly and persist for some time.

The most common allergens in such conditions are drugs, e. g., butyn, pontocaine, atropine, sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and hydrous wool fat. Also, cosmetics, such as nail enamel, rouge, powder, lash darkener and hair dye, are common offenders. Foods and other agents may act in a similar manner.

The history in cases of allergic dermatitis and keratoconjunctivitis is of recurrent attacks of redness and swelling of the eyelids accompanied

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From the Department of Ophthalmology, State University of Iowa College of Medicine.

Read at the Seventy-Eighth Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 1, 1942.

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4. Manksch, H.: Ztschr. f. Augenh. **91**:343, 1937.
5. Klar, R.: Klin. Monatsbl. f. Augenh. **104**:205, 1940.

by congestion of the globe. In rare cases a history of recurrent "corneal ulcers" is obtainable. The patient complains usually of lacrimation and often of a mucopurulent discharge. Itching is frequently present, and occasionally actual pain is described.

Examination reveals redness, edema and desquamation of the skin of the eyelids. In the early stages the skin may be moist and weeping, but usually it is discolored, dry and scaly. The palpebral conjunctiva and the conjunctiva of the fornices are congested, thickened as a result of papillary hypertrophy and in some cases studded with follicles. The bulbar conjunctiva is injected and may be chemotic.

In those rare cases in which keratitis occurs, the lesion develops rapidly, i. e., within a few hours. The patient complains of redness of the globe, lacrimation, photophobia and discomfort or even actual pain. In the cornea one or more dense yellow infiltrates or areas of necrosis may be seen just within the limbus, with a narrow zone of normal cornea separating the limbus from the lesion. It is important to recognize that these areas are infiltrates or areas of subepithelial necrosis and not ulcers. They do not stain with fluorescein. As seen with the biomicroscope, they appear as localized areas of necrosis in the superficial and middle layers of the corneal stroma. In association with such lesions there is mild or moderately severe iritis.

The diagnosis is difficult, but one should always consider the possibility of allergy in patients with recurrent attacks of dermatitis of the lids, conjunctivitis and superficial infiltrates or areas of necrosis in the peripheral areas of the cornea. Scrapings from the conjunctiva may or may not show a local eosinophilia. It is often extremely difficult to determine the agent. The history is of great importance—one must make inquiries as to the use of drugs in or about the eyes, the use of cosmetics, contact with foods which might reach the lids or conjunctiva and contact with other possible offending agents. Tests for hypersensitivity to suspected specific agents may be made by means of the patch test, i. e., application of the agent to the skin of the forearm or the region of the lids for a period of twenty-four to forty-eight hours. Or one may drop small amounts of certain agents into the conjunctival sac. Whichever test is used, if the patient is allergic a local inflammation develops at the site of contact. The substance involved of course does not always prove to be the cause of the ocular inflammation, since one may be sensitive to more than a single allergen. The usual method of testing for allergy, by injection of the allergen or its application to scratches in the skin of the back, has not been very satisfactory in our experience. Another method which may be used in the determination of the agent is the removal, one by one, of all suspected allergens.

As an interesting and typical example of allergic keratoconjunctivitis, the following case is reported:

Case 1.—W. B., a youth aged 20 years, was seen because of recurrent attacks of dermatitis of the lids, conjunctivitis and "corneal ulcers." Examination revealed red, dry, scaly lids and in the right eye a red, thickened palpebral conjunctiva, a dense yellow superficial infiltrate or necrotic area in the lower periphery of the cornea and mild iritis (fig. 1). Allergy was not suspected at this time; consequently, the patient was treated with mild chemical cauterizing agents and scopolamine hydrobromide and was given foreign protein therapy. After a rather slow recovery the eye was normal, but three months later a similar attack occurred in both eyes. Allergy was now considered as a probable cause, but no specific agent could be found. The patient was asked to keep in mind the possibility of hypersensitivity and to report any suspicious agents. A

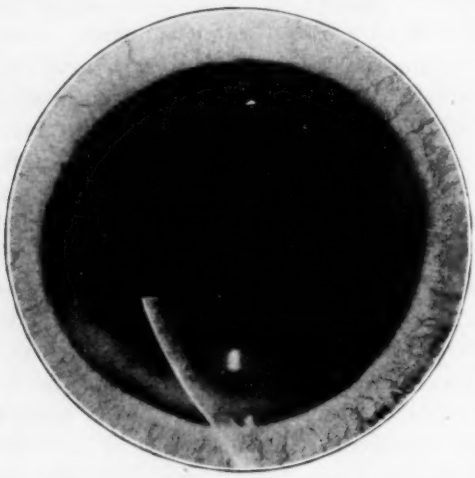

Fig. 1 (case 1).—Necrosis or infiltrate in the corneal stroma in a case of allergic keratoconjunctivitis due to oranges.

few weeks later, while he was peeling an orange, something squirted into his eyes and immediately they began to burn and became red and congested. Overnight a typical dermatitis and keratoconjunctivitis developed. An orange peel patch test on the forearm resulted within five or six hours in a red indurated area 5 cm. in diameter in the center of which were three large vesicles. The patient was told to avoid oranges, and no further trouble was reported until he ate some orange marmalade one evening. The following day he appeared with typical dermatitis, conjunctivitis and corneal infiltrate. Some time later he inadvertently indulged in punch which contained oranges, and another attack developed. Since then there has been no further trouble.

In another interesting example of this disease, butyn proved to be the offending agent:

Case 2.—A woman aged 41 complained of recurrent "sore eyes" and "corneal ulcers" over a period of five years. When she was first seen the lids of the

right eye were red and swollen, the conjunctiva was congested and thickened, there was a profuse discharge and near the nasal limbus was a large crescentic infiltrate or area of necrosis in the cornea. Since there was a history that eye drops had been used over a long period, a drug was suspected as the allergen. A drop of butyn sulfate was instilled into the conjunctival sac of the unaffected eye, and soon the conjunctiva became red and edematous. Lacrimation and later a profuse discharge developed. The lids were red and swollen, and by the following day typical corneal infiltrates or necrotic areas had appeared (fig. 2). Removal of the allergen resulted in a rapid and complete cure.

Three other cases have been observed; the keratoconjunctivitis in one was the result of contact with hydrous wool fat used as a base for an ophthalmic ointment, in another was believed to be due to use of a proprietary inhalant and in the third resulted from wearing of a recently purchased fur coat. Several cases of dermatitis and conjunctivitis without corneal complications have been observed.

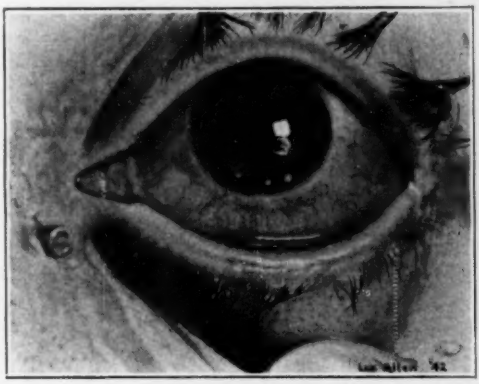

Fig. 2 (case 2).—Corneal infiltrates or necrotic areas in a case of allergic keratoconjunctivitis due to butyn.

The prognosis in this disease is good if the etiologic agent can be found. If it cannot be determined, one must expect recurrences. If the specific allergen is found and further contact is avoided, the disease disappears. Sometimes desensitization to the specific agent is of benefit; this is accomplished by weekly intradermal injections of the allergen, small at first and gradually increasing in amount.

CONCLUSIONS

Allergic dermatitis of the lids is not uncommon, but allergic keratoconjunctivitis is rare. It is difficult to determine the etiologic agent, but one commonly suspects such allergens as drugs, cosmetics and foods. Characteristically the conjunctiva is congested and thickened, and perhaps the seat of folliculosis, and the cornea shows yellow, opaque areas of necrosis or infiltration in the region just within the limbus.

These areas are situated in the superficial and middle layers of the corneal stroma and are probably necrotic, since allergic inflammation is of the necrotizing type. Eosinophils may or may not be found in the discharge or in scrapings from the conjunctiva.

Diagnosis is made by clinical appearances, and the etiologic agent is determined by patch tests or elimination of contact with suspected agents. Treatment is by removal of the allergen if possible or by desensitization with small intradermal injections of the offending agent.

State University of Iowa.

GEORGE BERKELEY AND "AN ESSAY TOWARDS A NEW THEORY OF VISION"

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PHILADELPHIA

Despite the high place assigned by Aristotle to the eye as the chief organ through which objective reality is given and to sight as the most comprehensive of all the senses, from the earliest recorded times the mysteries of sight have been the wonder of men. For ages the eyeball was so imperfectly dissected and its physiology so little understood that it could not be ascertained exactly which were the recipient and which the percipient portions. All sorts of ideas prevailed. Galen's dictum that the crystalline lens is the essential element was not disproved until the middle of the sixteenth century. Leonardo likened the organ of vision to a "box," the "camera obscura," but it was Maurolyco (1494-1577) who demonstrated that sight is accomplished by means of the retina.

By about the middle of the seventeenth century optical science had so progressed that physicists became convinced that the eyeball is like a box into which light enters after the refraction of its rays by the convex surfaces of the cornea and the crystalline lens, by which the rays are so adapted as to be focused to a point on the interior walls of the box—on the retina; thus confirming the supposition of Leonardo. Throughout the century speculation was rife and most various as to the sources of the functions of the eye and as to the seat of vision. It was the philosophers, however, as well as the physicists, who were the chief investigators and theorizers; because their studies were chiefly on the refraction of the curved surfaces, they commonly achieved only geometric results. All observers, however, were concerned with the discussions as to whether an appreciation of the field of view and the ability to comprehend the visual reactions within it were innate or acquired properties.

It is true that Kepler, Descartes, Newton and John Locke had sought an explanation of the manner by which the external world is perceived and the means employed to arouse one's judgment of the relation which the objects perceived bear to one another, but their chief endeavors were applied to the comprehension of the processes by which the images are interpreted by the individual.

Read at the Seventy-Eighth Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 1, 1942.

Early in the eighteenth century the philosophic world was startled by the appearance, in 1709, of "An Essay Towards a New Theory of Vision," published by George Berkeley, of Dublin, Ireland.

The author's design of the "Essay" was "to show the manner wherein we perceive by sight the distance, magnitude, and situation of objects. Also to consider the difference there is betwixt the ideas of sight and touch, and whether there be any idea common to both senses." An

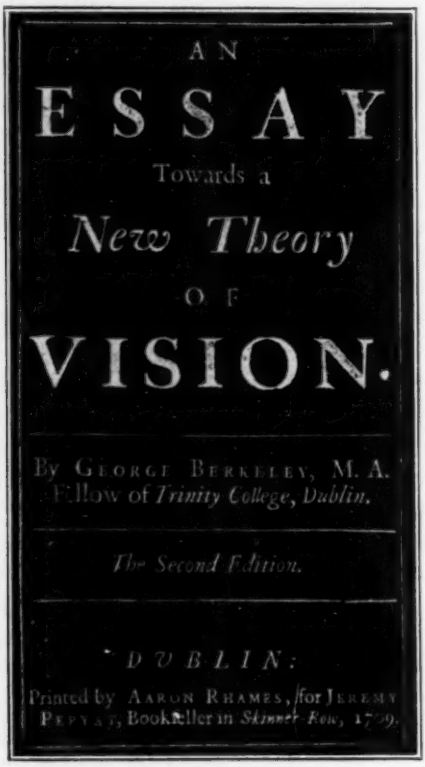
AN
ESSAY
Towards a
New Theory
OF
VISION.
By GEORGE BERKELEY, M. A.
Fellow of *Trinity College, Dublin.*
The Second Edition.
DUBLIN:
Printed by AARON RHAMES, for JEREMY
PEPYAT, Bookseller in *Skinner Row*, 1709.

Fig. 1.—Title page of the "Essay."

appeal was made also to consciousness. The author attempted to analyze that "of which we are conscious in seeing" and suggested what "we are conscious of in touch also." These are "the underlying factors of our visual appreciation." He made no observations of the optical and physiologic phenomena; the "Essay," therefore, is distinctly a contribution to the psychologic analysis of the facts of vision and not a deduction from physical experiments in optics or ocular physiology.

The problem as expressed was to seek an explanation of how it is "that sensations, or 'ideas,' of colour can inform us, the consciousness of what we understand as 'vision.'"

It is not my intention to make a systematic analysis of Berkeley's essay on vision, but only to indicate briefly certain of the theorems, which in general are attempts toward an understanding of the psychology of sensations. I quote the opening paragraphs of the "Essay" so that the reader will have an idea of what Berkeley proposed to demonstrate:

1. My design is to show the manner wherein we perceive by sight the distance, magnitude, and situation of objects. Also to consider the difference there is betwixt the ideas of sight and touch, and whether there be any idea common to both senses. (In treating all of which, it seems to me, the writers of optics have proceeded on wrong principles.)

2. It is, I think, agreed by all that distance of itself, and immediately, cannot be seen. For distance being a line directed endwise to the eye, it projects only one point in the fund of the eye—which point remains invariably the same, whether the distance be longer or shorter.

3. I find it also acknowledged that the estimate we make of the distance of objects considerably remote is rather an act of judgment grounded on experience than of sense. For example, when I perceive a great number of intermediate objects, such as houses, fields, rivers, and the like, which I have experienced to take up a considerable space, I thence form a judgment or conclusion, that the object I see beyond them is at a great distance. Again, when an object appears faint and small which at a near distance I have experienced to make a vigorous and large appearance, I instantly conclude it to be far off. And this, it is evident, is the result of experience; without which, from the faintness and littleness, I should not have inferred anything concerning the distance of the objects.

4. But, when an object is placed at so near a distance as that the interval between the eyes bears any sensible proportion to it, the opinion of speculative men is, that the two optic axes (the fancy that we see with only one eye at once being exploded), concurring at the object, do there make an angle, by means of which, according as it is greater or lesser, the object is perceived to be nearer or farther off.

He referred to a peculiar organic sensation accompanying the adjustment of the eye to the various objects presented to it (sections 16 to 20), thus vaguely conceiving the physiologic reaction in what is now known as accommodation.

He was aware of the confusion likely to arise when the eye receives rays from different objects, and he noted the strain put forth in its efforts to make distinct and to comprehend the characteristics of the objects viewed. He spoke repeatedly of "straining of the eyes." Can it be that the early inventors of the term eyestrain adopted Berkeley's reference to the "organic sensation of straining" for the group of symptoms so frequently found accompanying ametropia?

Berkeley, in discussing the apparent place of objects, as set forth by Isaac Barrow (1630-1679) in his lectures on optics published in 1674, observed that the chief circles formed by the rays which do not come to a focus on the retina produce the same confusion in the eye whether they cross one another before they reach the retina or afterward. Judg-

ment concerning distance will be the same in the two cases, without any regard to the place from which the rays originally issued, so that when an object recedes from a lens held by an observer, the confusion which always accompanies the nearness of an object increases and the mind judges that the object comes nearer.

It must be remembered that while much was known about myopia in Berkeley's time, nothing was exactly stated until the opening of the nineteenth century. In all the years from Alhazen until quite a hundred years after the "Essay," that is, in the early 1800's, hypermetropia was not recognized or its condition of refraction suspected.

Berkeley declared that in a person's comprehension of what is visible to himself, he is primarily attracted by the color of the object. Perception of color is facilitated when accompanied by the sense of touch, by which he ascertains whether the object is hard or soft, rough or smooth, shallow or deep, round or square and near or distant. The comprehension of these qualities exists in his mind, and the reaction thereto obtains within his own consciousness.

Accordingly, all sight is based on experience. In support of this contention, Berkeley told repeatedly of persons believed to have been blind at birth whose comprehension exhibited uncertainties after the establishment of sight on the removal of obstruction by operation. He said that to such persons sight may have seemed to be "in their eyes, or rather in their mind." They would at first have no idea of distance by sight; the objects would seem to them like a new set of thoughts.

Berkeley would not accept the dictum that sight depends on "geometry." For a long time workers in optics offered this dictum as a sufficient explanation in estimating convergent and divergent rays lighting on the recipient elements of the eyeball and focused on the deeper percipient fund of the eye. He believed that all such geometric "Extensions are invisible, but Colour, on the contrary, is a pure sensation and cannot exist extraorganically in space." Therefore, sight is further proved to be the result of a combination of senses.

"Distance" is judged by the effort and the succession of muscular feelings experienced by the movement of the eyes in fixing their gaze from point to point on the object under observation. The efforts of "'touch' and 'tactual' reactions" together with those connected with "locomotive experience" are concerned in all intelligent estimates of distance.

The "Essay" is arranged in paragraphs, or "Sections," one hundred and sixty in number, without captions or orderly classification, in clear, charming, plain, easy to read English and without extraordinary scientific words and expressions. While it is not always possible to derive the same meaning from some of the words as that which was implied by the author in his use of them, the essay is singularly free from pre-

tended facts and involved metaphysical abstractions and is a serious contribution to human psychology. Likewise, it is not always easy to accept the substance section by section, yet together the sections present a continuous chain of thought, singularly and lucidly linked, leading one on irresistibly page after page. There is a most interesting chapter the subject of which is repeated several times. This relates to the problem of the variations in the moon's appearance when horizontal and when high overhead. The moon seems larger and less distinct when horizontal, because of the haziness of the atmosphere near the ground, and smaller but more brilliant when vertical, through the clearness of the atmosphere.

The "Essay" was not the author's first work. In 1707 he published two mathematical tracts in Latin. The "Essay" was followed by a "Treatise Concerning the Principles of Human Knowledge." When it was published inquiries began to be made as to who had written these works. Who was Berkeley and whence came he? It was learned that he was born in Ireland, near Thomastown, in County Kilkenny, on March 12, 1685, of English ancestry but of uncertain antecedents. His early education was at a local school, and at the age of 15 he entered Trinity College, Dublin. During his student days he organized a society to promote philosophical investigation. Even this early he had entered the ranks of the great thinkers of all times. "He came forth the most subtle and accomplished philosopher of his time, almost from darkness." It is remarkable that one so young as Berkeley could have created and developed a system of speculative reasoning such as is set forth in the "Essay." He was without any laboratory or other equipment. His reading had been unusually extensive, and his observation of human manifestations of the senses was exact and searching. The "Essay" was completed and published by him when he was less than 25 years of age. It is not known how long Berkeley had been in preparing it. Many years after his death a "commonplace book" was found containing his thoughts and comments on what he had been reading years before the period 1707 to 1710. A remarkable precocity.

While a second edition of the essay was printed within the year of the original publication, at first the "Essay" drew little attention; indeed, for twenty years or more but few allusions were made to it, mostly in the form of letters to the *Gentlemen's Magazine*. In the *Philosophical Transactions* for 1728 there was reported Cheselden's account of his study of the visual experiences recounted by the lad whose blindness he had relieved by the discission of cataracts—after which attention was brought to Berkeley. In time he won the admiration of learned scientists and philosophers, who regarded him as the successor of Locke. It is true that for the rest of the century he was criticized and his inconsistencies pointed out; yet he ably fought all contests. Berkeley suffered

more perhaps than any other great modern philosopher from misunderstanding. He lived through the most prosaic and least metaphysical age since the revival of letters. In 1733, in response to an anonymous letter which appeared in a Dublin newspaper, Berkeley published another article, entitled "The Theory of Vision, or Visual Language, . . . Vindicated and Explained." This he hoped might serve as a commentary on the early "Essay." The doctrine became a commonplace among the

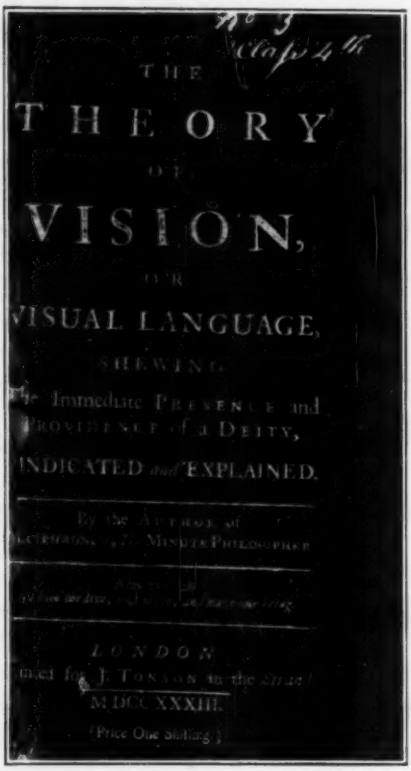
THE
THEORY
OF
VISION,
OR
VISUAL LANGUAGE,
SHEWING
The Immediate PRESENCE and
PROVIDENCE of a DEITY,
INDICATED and EXPLAINED.
By the Author of
LONDON
Printed for J. TONSON in the
M.DCC.XXXIII.
(Price One Shilling.)

Fig. 2.—Title page of the sequel to the "Essay."

French, and, in time, influenced the English and Scotch philosophers and psychologists also, who acknowledged it to be a true discovery in metaphysics.

George Berkeley may be considered to have been the most engaging and useful man in Ireland in the eighteenth century. His was a mind of extraordinary ingenuity and intrepidity. His intellectual growth was remarkable. Writing was easy for him. I shall not here enumerate his product. The "Essay" was the first of his metaphysical output. Besides having philosophical interests, he was a man of affairs. His associates

in Ireland and England, as well as those of importance on the Continent, were the intellectual and forceful of his day, statesmen as well as men of letters.

Berkeley may be called the patron of education in America. He should be of interest to Americans. He conceived a project for the establishment of a college in the Bermudas for the purpose of educating missionaries to undertake to civilize the aborigines of the new country. He sailed for America in 1728. The course of his voyage was deflected,

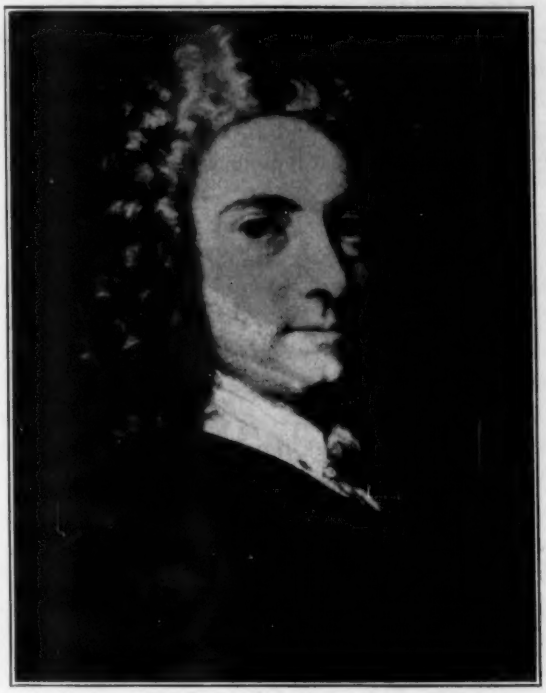

Fig. 3.—George Berkeley about 1720.

and he landed at Newport, R. I. There he resided for three years, during which he mingled with the foremost men of the colony, and out of that sojourn grew an abiding interest in education to the extent of his becoming the patron of Yale and Harvard colleges. For years he contributed largely to the library of each. A disastrous fire destroyed Harvard's library, but Yale's has been preserved and can be consulted today. While at Newport he composed one of his works still famous in philosophy.

The project of the Bermuda college failed of promised support by king and commons, and Berkeley was forced to give up his scheme.

On his return home, in 1732, he was speedily advanced in ecclesiastical honors. About the time the "Essay" was published he was ordained in holy orders. He became dean of Derry (Londonderry, Northern Ireland) in 1724, and in 1734 bishop of Cloyne, near Cork, in the South of Ireland. Throughout Berkeley's life his was an unobtrusive practical piety, and as long as he lived he remained free from ecclesiastical and political bias.

His interest in the health and livelihood of the Irish peasantry was unbounded. Years of devastating famine occurred. Berkeley's service as an efficient public health apostle is worthy of a special chapter in the history of Great Britain, and consideration might be given to the kindly bishop's principles even today. In this period Berkeley's interest in the efficacy of "Tar water," the medicinal qualities of which he had learned in America, became manifest, and for almost a century the question of the use of tar water agitated the medical profession and humanitarians in general.

The "Essay" and its sequel fell into the background after a fierce debate, which lasted fifty years or so. Today the "Essay" is rarely if ever mentioned by philosophers and psychologists. Systematic ophthalmologic and optical works, with the exception of von Helmholtz', may be searched with little success, probably because the "Essay" is a psychologic analysis of visual perception, the purpose being to show that the act of seeing is an act of interpretation of what is before one in space, depending on conscious intelligence and not on the observing of physiologic or optical phenomena.

In all his observations Berkeley relied on the doctrine of the creation and development in visual space of "ideas," much as had Locke. Such ideas Berkeley believed are formed by the intelligent comprehension of what the phenomena generate in the individual, while the source of that comprehension is in God, the Creator of all things.

Although the "Essay" is limited in its application to the conception of sight and the benefits derived therefrom, its substance has entered into the fabric of metaphysical science. Goethe, in his studies in sight and color, employed methods similar to those Berkeley observed. I did not, however, find allusions to the Irish bishop's "Essay" in any of his writings.

Hirschberg, in the Graefe-Saemisch "Handbuch," remarked that in the general gathering of data Berkeley had not sufficiently appreciated the observations of German investigators.

Von Helmholtz, in part 3 of "Handbuch der physiologischen Optik," referred to Berkeley's study of the influence of memory on visual perceptions which occur so rapidly that unless one is on the lookout for them, one is not conscious of their existence.

I dare say readers of Fraser's collection of Berkeley's works pass over the "Essay" and the "tar water" paper. The volumes in my possession have had rather hard usage, as have those I have consulted at libraries, yet the pages of those chapters had not been cut until I received them.

It is not my intention to advocate the acceptance of Berkeley's theory as necessary for the working ophthalmologist. Philosophers in the first half of the eighteenth century, in their efforts to learn how the human being acquired sight, must have relied on Berkeley's "Essay" as well as on Locke's psychologic writings for the bases of their discussion.

I wish, however, that a group of learned ophthalmologists might gather together with philosophers and psychologists to interpret in modern thought this juvenile production. The "Essay" was the foundation of Berkeley's more mature works, and my wish cannot readily be realized because such a study would require a reading of his later works to obtain his complete exposition.

In the light of modern research, to obtain a practical demonstration of Berkeley's proposition observation should be made of the sight of infants and when possible of lower animals also, as their conditions would be primitive. Then a study should be made of intelligent helpful adolescents blind from birth, with a blindness almost absolute, when the blindness has been relieved by operation and sight is beginning to be established. Such persons should become suitable subjects and yield great service to science. They would have been without any visual knowledge of distance, space, the sun and the stars and all else both near and remote.

I have given but a meager review of Berkeley's theory of vision, which for a century met with the widest acceptance by philosophers and metaphysicians. I am not a philosopher, much less a metaphysician. What I have presented is incomplete and therefore unsatisfactory. In my perusal of the "Essay" and its sequel, I was reminded of the imaginative teachings of that mystic, Johannes Müller, in his "Comparative Physiology of Vision." To those who have had no previous knowledge of the writings of Bishop Berkeley, I trust that what I have given may serve as an incentive to them to inquire further for themselves. In conclusion, I would suggest that they read in Helmholtz' "Popular Lectures on Scientific Subjects"[1] the chapter on "The Perception of Sight," wherein are references to the place that color, touch and ocular movement occupy in the establishment of sight, the sense which enables one to arrive at a knowledge of the external world, and to the effects in the comprehension of mind and matter resulting from experience.

1. Helmholtz, H.: Popular Lectures on Scientific Subjects, London, Longmans, 1873.

Copies of the original publications of Bishop Berkeley are now scarce, yet most old libraries possess them. No collection of his works was made until fifty years after his death. A complete collection, including articles then newly discovered, was edited by A. C. Fraser in 1871.[2] A neat, handy edition containing the "Essay" was issued in Everyman's Library in 1910,[3] with later reprintings up to 1938.

Fraser's collection is loaded with notes and with references extending from the most ancient times to 1870. I have not burdened this brief article with my own lists. Interesting critical biographies are in all cyclopedias; I would especially mention Leslie Stephen's article in the "Dictionary of National Biography."

317 South Fifteenth Street.

2. Fraser, A. C.: Life and Letters of George Berkeley, London, Oxford University Press, 1871.

3. Berkeley, G.: New Theory of Vision and Other Select Philosophical Writings, Everyman's Library, no. 483, New York, E. P. Dutton & Co., Inc., 1910.

EFFECTS OTHER THAN ANTI-INFECTIOUS OF SULFONAMIDE COMPOUNDS ON EYE

MOACYR E. ALVARO, M.D.
SÃO PAULO, BRAZIL

According to Long and associates,[1] ocular involvement is a rare complication in therapy with sulfonamide compounds. As far as could be determined, ocular complications, although they indicated the advisability of stopping the treatment, did not have the same mandatory importance as other complications, such as hepatitis, leukopenia with granulocytopenia, acute agranulocytosis and hemolytic anemia.

Nevertheless, the data found in the ophthalmologic literature and occasionally elsewhere regarding ocular involvement as a consequence of the use of sulfonamide compounds are numerous enough to suggest the necessity for a systematic study of the subject.

PENETRATION AND DISTRIBUTION OF SULFONAMIDE COMPOUNDS IN THE EYE

Sulfonamide compounds given orally reach the eye as soon as fifteen minutes after they are taken (Bellows and Chinn [2]) and arrive at their maximum concentration in the ocular tissues about the sixth hour. They are found in the tears (Venco [3]) and can still be traced in the ocular tissues more than thirty-six hours after they have ceased to be taken.

The concentration varies considerably according to the kind of drug and is not the same in the different parts of the eye. Thus, sulfanilamide is found in the aqueous in a concentration 67 per cent of that in the blood in rabbits (Liebman and Newman [4]), in a concentration of 61 per cent in dogs (Bellows and Chinn [5]) and in a concentration of 78.7

From the Department of Ophthalmology, Escola Paulista de Medicina.

Read before the Section on Ophthalmology at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N. J., June 10, 1942.

1. Long, P. H.; Haviland, J. W.; Edwards, L. B., and Bliss, E. O.: Toxic Manifestations of Sulfanilamide and Its Derivatives, J. A. M. A. **115**:364 (Aug. 3) 1940.

2. Bellows, J. G., and Chinn, H.: The Distribution of Sulfanilamide in the Eye, Am. J. Ophth. **23**:816 (July) 1940.

3. Venco, L.: Sulla presenza della sulfanilamide nel liquido lacrimale, Ann. di ottal. e clin. ocul. **67**:30 (Jan.) 1939.

4. Liebman, S. D., and Newman, E. H.: Distribution of Sulfanilamide and Its Derivates Between Blood and Aqueous, Arch. Ophth. **26**:472 (Sept.) 1941.

5. Bellows, J. G., and Chinn, H.: The Distribution of Sulfanilamide in the Eye, J. A. M. A. **112**:2023 (May 20) 1939.

per cent in cats (Scheie and Souders [6]), whereas sulfapyridine (2-[para-aminobenzenesulfonamido]-pyridine) is found in a slightly smaller concentration (64 per cent) in rabbits according to Liebman and Newman and in a somewhat higher concentration (68 per cent) according to Meyer, Bloch and Chamberlain [7] and in a concentration of 81 per cent in cats according to Scheie and Souders.[6] Sulfathiazole (2-[para-aminobenzenesulfonamido]-thiazole) is found in a much smaller concentration, 17 per cent in rabbits (Liebman and Newman [4]) and 18.4 per cent in cats (Scheie and Souders [6]). Finally, sulfadiazine (2-[para-aminobenzenesulfonamido]-pyrimidine) is found in the aqueous of rabbits in a concentration 55 per cent of that in the blood, while cats show a concentration of 75 per cent. Postmortem studies on human beings revealed proportions somewhat similar to those found in animals. Concentrations were found of 51 per cent for sulfapyridine and 22 per cent for sulfathiazole.

Locally used, by instillation of a solution or by insufflation of the powdered substance on the cornea or into the conjunctival sac, sulfonamide compounds penetrate into the eye, too, but the concentration in the aqueous thus obtained varies considerably according to the nature of the drug and according to the method used. Mengel [8] dropped a concentrated solution of sulfanilamide (0.8 per cent) into a glaucomatous blind eye. Three drops was instilled every fifteen minutes for six doses and then 3 drops every five minutes for six doses before operation. The concentration of sulfanilamide then found in the aqueous was less than 0.1 mg. per hundred cubic centimeters, whereas after giving sulfanilamide orally the same author found concentrations in the aqueous of 1.5 to 3.2 mg. per hundred cubic centimeters. P'an,[9] applying powdered sulfanilamide to the cornea during one hour, obtained larger concentrations than those obtained by giving medium doses of sulfanilamide orally. He found, too, that using 100 mg. of powdered sulfanilamide on the cornea during one hour does not lead to any absorption of the drug into the body, as hardly any can be traced in the blood. Bellows and Chinn,[10] using ointments containing sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine applied at thirty minute intervals for six hours to rabbits'

6. Scheie, H. G., and Souders, B. F.: Penetration of Sulfanilamide and Its Derivatives into the Aqueous Humor of Eye, Arch. Ophth. **25**:1025 (June) 1941.

7. Meyer, K.; Bloch, H. S., and Chamberlain, W. P.: The Distribution of Sulfapyridine Between Blood, Aqueous Humor, and Cornea, Am. J. Ophth. **24**: 60 (Jan.) 1941.

8. Mengel, W. G.: Determination of Sulfanilamide in Aqueous and Vitreous After Conjunctival and Oral Administration, Arch. Ophth. **22**:404 (Sept.) 1939.

9. P'an, S. Y.: Distribution of Sulfanilamide in Ocular Fluids and Tissues After Local Application, Proc. Soc. Exper. Biol. & Med. **46**:31 (Jan.) 1941.

10. Bellows, J. G., and Chinn, H.: Corneal Penetration of Sulfanilamide and Some of Its Derivates, Arch. Ophth. **27**:34 (Jan.) 1942.

and dogs' eyes, found that the concentration of the drugs in the aqueous was as follows (in mg. per hundred cubic centimeters): for the dogs—sulfanilamide 6.1, sulfapyridine 1.6, sulfathiazole 0.3 and sulfadiazine 0.7; for the rabbits—sulfanilamide 31.1, sulfapyridine 2.3, sulfathiazole 2.6 and sulfadiazine 3.0. Powdering sulfanilamide on the corneas, Bellows and Chinn found a concentration of 6.6 mg. for the dogs and 88 mg. for the rabbits. P'an found a concentration of 22 mg. per hundred cubic centimeters in the aqueous of human beings after local use of sulfanilamide. Meyer, Bloch and Chamberlain [7] tested the power of adsorption of the cornea and found that in vitro the cornea will hold sulfanilamide in a concentration three and a half to four times stronger than the buffer solutions of sulfanilamide and one and a quarter times stronger than the buffer solutions of sulfapyridine. Robson and Tebrich,[11] using sodium sulfacetimide, which is much more soluble, found that the penetration through the cornea was considerable.

Instilling a 15 per cent solution of sodium sulfacetimide into the eyes of rabbits, 1 drop every five seconds for five minutes, I found that the concentration of the drug in the aqueous was 2.23 mg. per hundred cubic centimeters. When 1 drop of a solution of sodium dioctylsulfosuccinate was instilled previous to the instillation of sodium sulfacetimide, a concentration of 8.68 mg. was obtained. When 0.9 cc. of sodium sulfacetimide in a 30 per cent solution was injected subconjunctivally into rabbits, a concentration of 13.14 mg. was found in the aqueous thirty minutes afterward.

Sulfonamide compounds are not found in equal concentrations in the several parts of the eye. Bellows and Chinn,[12] experimenting with dogs, found the following concentrations [12a] after oral administration of the drug: For sulfanilamide, with a concentration in the blood of 18.0 mg. per hundred cubic centimeters, the choroidoretinal tissue had 15.2 mg., the cornea and sclera 13.4 mg., the aqueous 10.9 mg., the vitreous 8.4 mg. and the lens 2.7 mg.; for sulfapyridine, with a concentration in the blood of 6.1 mg. the sclera had 7.0 mg., the cornea 6.8 mg., the choroidoretinal tissue 6.3 mg., the vitreous 5.8 mg., the aqueous 4.9 mg. and the lens 1.1 mg.; for sulfathiazole, with a concentration in the blood of 7.4 mg., the sclera had 10.4 mg., the choroidoretinal tissue 4.9 mg., the cornea 2 mg., the vitreous 0.9 mg., the aqueous 0.4 mg. and the lens none.

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11. Robson, J. M., and Tebrich, W.: Penetration of a Water-Soluble Sulfonilamide, Sodium Sulfacetamide Into the Eyes of Rabbits, Chem. Abstr. **36**:1389 (March) 1942.

12. Bellows, J. G., and Chinn, H.: Penetration of Sulfathiazole in Eye, Arch. Ophth. **25**:294 (Feb.) 1941.

12a. Values in the blood and the aqueous are per hundred cubic centimeters; those in other tissues, per hundred grams of moist tissue.

CHANGES IN THE EYES DUE TO SULFONAMIDE COMPOUNDS

Several changes have been reported as being the result of the use of sulfonamide compounds: (1) palpebral edema, (2) conjunctivitis, (3) chemosis, (4) scleral reaction, (5) cells in the aqueous and iritis, (6) mydriasis, (7) cataract, (8) changes in angioscotomas, (9) edema of the retina, (10) reduction of the visual fields, (11) retinal hemorrhages, (12) optic neuritis, (13) undefined or unidentified blurred vision, (14) transient hyperopia, astigmatism and myopia and (15) changes in accommodation.

Palpebral edema was mentioned by Esterman,[13] who saw swelling of the lids accompanied by transient myopia in a patient taking 1.3 Gm. of sulfanilamide a day.

Conjunctivitis was reported by Volini, Levitt and O'Neil [14] as having been seen in a patient using sulfathiazole who had erythema and other cutaneous disorders. Long and Haviland [15] reported 4 cases of conjunctivitis following the use of sulfathiazole.

Chemosis was found by Hornbogen,[16] together with transient myopia and astigmatism, in a woman 28 years old who had taken 3 Gm. of sulfanilamide a day for fourteen days. In the case of palpebral edema reported by Esterman [13] there was chemosis, too, and Valdeavellano [17] mentioned chemosis in a woman who had taken sulfanilamide for twelve days and who also showed transient myopia and optic neuritis.

A scleral reaction accompanying dermatitis and conjunctivitis was mentioned by Long and Haviland.[15a]

Cells in the aqueous were found by Semadeni [18] in a man aged 23 who had taken 0.90 Gm. of sulfanilamide and 0.45 Gm. of the original prontosil (the hydrochloride of 4-sulfamido-2′,4′-diaminoazobenzene) the same day. This patient also showed transient myopia.

Van Lint [19] mentioned iritis which occurred in a patient with gonorrhea undergoing a combined treatment with vaccine and sulfanilamide.

13. Esterman, B., in discussion on Bailey.[44]

14. Volini, I. F.; Levitt, R. O., and O'Neil, H. B.: Cutaneous and Conjunctival Manifestations of Sulfathiazole Intoxication, J. A. M. A. **116**:938 (March 8) 1941.

15. (*a*) Haviland, J. W., and Long, P. H.: Skin and Ocular Reactions in Sulfathiazole Therapy, J. A. M. A. **114**:2505 (June 22) 1940. (*b*) Long, Haviland, Edwards and Bliss.[1] (*c*) Haviland, J. W., and Long, P. H.: Skin, Conjunctival and Scleral Reactions in Course of Therapy with Sulfathiazole, Bull. Johns Hopkins Hosp. **66**:313 (May) 1940.

16. Hornbogen, D. P.: Transient Myopia During Sulfanilamide Therapy, Am. J. Ophth. **24**:323 (March) 1941.

17. Valdeavellano, J.: Los sulfamidabos en oftalmologiá y algunos de sus accidentes, Rev. méd. peruana **11**:556 (Nov.) 1939.

18. Semadeni, B.: Transitorische Myopie nach Sulfanilamide und Prontosiltabletten, Ophthalmologica **103**:109 (Feb.) 1942.

19. van Lint, A.: Iritis au cours du traitement d'une blennorragie chronique par sulfamide et vaccin, Bull. Soc. belge d'opht. **79**:150 (March) 1940.

Mydriasis is mentioned in almost every case of transient myopia, but in the great majority of cases the pupils reacted normally and showed no deformity.

A sudden opacification of the lens in a case of iridocyclitis treated with sulfanilamide was mentioned by van Lint and Alaerts.[20]

Rosenthal [21] reported experiments in measuring the angioscotomas in patients with normal eyes before and after the use of sulfanilamide. The angioscotomas of 1 patient were mapped, he was given 8.75 Gm. of sulfanilamide in twenty-two hours and another test of the angioscotomas was made. After another thirteen and one-half hours, during which sulfanilamide was given until the total amount reached 12.64 Gm., a third mapping was performed. The administration of sulfanilamide was then stopped, and four days later the angioscotomas were mapped again. A similar method was used on another patient, but the total amount of sulfanilamide was only 11.66 Gm. and maps were made when 5.83 Gm. had been given and forty-eight hours and one hundred and twenty-four hours after use of the drug was discontinued. In both patients a narrowing of the angioscotomas occurred, and in both this change disappeared five days after use of the drug has been discontinued.

Edema of the retina has been mentioned by Herman, who examined Spellberg's [22] patient, a man aged 41 who had transient myopia after the use of 1.94 Gm. of sulfanilamide. He had discontinued use of the drug and had then taken 0.11 Gm. more. No general signs of intolerance appeared. With the proper correction his vision was normal. Valdeavellano [17] mentioned edema of the retina with transient myopia in a girl aged 18 after the use of sulfanilamide for twelve days both orally and parenterally. Signs of general intolerance had been noticed on the seventh day after the beginning of the treatment. No impairment of vision due to the retinal change could be detected.

Valdeavellano in 1 of his patients with transient myopia, a girl of 18 who had taken only 1.5 Gm. of sulfanilamide, found the visual fields restricted, especially for green.

Two patients with retinal hemorrhages were reported on by Goar.[23] One was a woman aged 34 who had taken 68 Gm. of sulfathiazole in seven days for pneumonia and who complained of blurred vision. In the fundus of each eye four small retinal hemorrhages could be seen. There

20. van Lint, A., and Alaerts, L.: Cataracte après sulfamides dans un cas d'iridocyclite, Bull. Soc. belge d'opht. **78**:134, 1939.

21. Rosenthal, C. M.: Changes in Angioscotomas Associated with Administration of Sulfanilamide, Arch. Ophth. **22**:73 (July) 1939.

22. Spellberg, M. A.: Toxicity of Sulfanilamide, Illinois M. J. **75**:366 (April) 1939.

23. Goar, E. L.: Retinal Hemorrhages Following the Ingestion of Sulfathiazole, Am. J. Ophth. **25**:332 (March) 1942.

was also a larger preretinal hemorrhage. No changes either in the blood or in the blood vessels could be detected. The hemorrhages were absorbed, leaving retinal pigmentation, and the vision was restored to 20/30 and 20/20, with a relative central scotoma in one eye. The other patient was a woman 37 years old who had taken 10.5 Gm. of sulfathiazole in one day and complained of blurred vision the next. Three weeks later she was examined by an ophthalmologist, who found that she had an area in the macula in which the retinal elements were destroyed and medial to that a cherry-colored spot of hemorrhage with the typical aspect of a preretinal hemorrhage. Her vision was then 20/400. A week later she was examined by Goar, who found that the blood had almost disappeared from the macular area, leaving a slight pigmentation. The vision was 20/30 — 2, and she had a small relative scotoma. There was no evidence of sclerosis in the blood vessels.

Another case of retinal hemorrhage after the use of sulfathiazole has been reported by Baker.[24]

Apparently the first ocular accident to be reported as due to use of a sulfonamide compound was that in Bucy's [25] case, in 1937, in which a girl of 16, under treatment for an infection caused by Streptococcus viridans, had taken 7.5 Gm. of sulfanilamide in two days. She had also taken acetylsalicylic acid, phenobarbital and ferrous sulfate. General signs of intolerance for the drug followed (cyanosis, etc.). Use of sulfanilamide was discontinued for three days, after which 1.8 Gm. was given in one day. That night she again showed symptoms of general intolerance and complained of blurred vision. Ophthalmoscopically, signs of optic neuritis could be seen, and there was a central scotoma. By stopping use of the drug, functional restitutio ad integrum was achieved in a short time. In Guerra's [26] case (which also occurred in 1937), a man aged 26 in two days had taken 17 Gm. of some drug of the sulfanilamide group for treatment of gonorrhea. When examined he had completely lost his vision, the pupils were enlarged, the veins in the retina were dilated and turgid and the disk appeared to be seen through a mist. Use of the drug was discontinued, and after twenty-seven days the vision had improved to 20/30. The visual field was still contracted, and both light sense and color sense were below normal. A third case of optic neuritis following the use of sulfanilamide was reported by Valdeavellano [17]; the patient, a girl of 18, had been using sulfanilamide orally and parenterally for twelve days. On the seventh day she had general symptoms of intolerance, and on the twelfth she complained of blurred vision.

24. Baker, J. P., Jr.: Sulfanilamide Therapy Followed by Hemorrhages in Fundus of Eye, Virginia M. Monthly **67**:562 (Sept.) 1940.

25. Bucy, P. C.: Toxic Optic Neuritis Resulting from Sulfanilamide, J. A. M. A. **109**:1007 (Sept. 25) 1937.

26. Guerra, B.: An. brasil. de oftal. **1**:478, 1942.

The changes in the disks were slight, and she recovered in a few days, after ceasing to use the drug. Still another case was reported by Bresser.[27] A youth 19 years old had taken 8 Gm. of sulfapyridine in three days, after which he complained of blurred vision. No refractive error could be detected, and he had ophthalmoscopic signs of optic neuritis. Seventeen days after he had discontinued use of the drug, his vision improved to 20/20 in both eyes.

Several cases of undefined or unidentified transient blurring of vision (Heinonen[28] and others) have been reported and probably could be classified with the cases of changes in refraction or possibly with those of optic neuritis and retinal involvement.

Changes in refraction comprise transient hyperopia, astigmatism and myopia. Thorne[29] mentioned hyperopia in a patient who had taken sulfanilamide and had to be given a correction of + 3.00 D. sph. ⊂ + 0.50 D. cyl., axis 180 to achieve normal vision. Astigmatism has been mentioned in connection with this case and with several cases of transient myopia (Hornbogen,[16] Bristow[30] and others). The astigmatic changes are generally small. Myopia is by far the most common ocular symptom observed as a consequence of toxic effects due to sulfonamide compounds, 36 well defined cases having come to my knowledge. The great majority of these have already been mentioned in the literature: Mattsson,[31] Gailey,[32] Missiroli,[33] Spellberg,[22] Spearman,[34] Friedman,[35] Blankstein,[36] Hornbogen,[16] Rittenhouse,[37] Bristow,[30] Brito,[38] Páez Allende,[39]

27. Bresser, J. S.: Personal communication to the author.

28. Heinonen, O.: Transitory Myopia After Use of Sulfanilamide, Duodecim **55**:552, 1939.

29. Thorne, F. H.: Symposium on the Use of Sulfanilamide in Eye Conditions, Am. J. Ophth. **22**:430 (April) 1939.

30. Bristow, J. H.: Temporary Myopia Due to Sulfanilamide, Arch. Ophth. **24**:799 (Oct.) 1940.

31. Mattsson, R.: Drei Fälle transitorischer Myopie, Acta ophth. **17**:314, 1939.

32. Gailey, W. W.: Transient Myopia from Sulfanilamide, Am. J. Ophth. **22**: 1399 (Dec.) 1939.

33. Missiroli, G.: Transitory Myopia After Ingestion of Sulfanilamide and Its Pathogenic Interpretation, Boll. d'ocul. **18**:50 (Jan.) 1940.

34. Spearman, M. P.: Transitory Myopia Following Sulfanilamide, Southwestern Med. **25**:13 (Jan.) 1941.

35. Friedman, B. B.: Acute Myopia Induced by Sulfanilamide, Am. J. Ophth. **24**:935 (Aug.) 1941.

36. Blankstein, S. S.: Transitory Myopia (Complication of Sulfanilamide Therapy), Am. J. Ophth. **24**:895 (Aug.) 1941.

37. Rittenhouse, E. A.: Myopia After Use of Sulfanilamide, Arch. Ophth. **24**:1139 (Dec.) 1940.

38. Brito, C.: Myopia transitoria produzida pela sulfanilamida, Arq. brasil. de oftal. **5**:27 (Feb.) 1942.

39. Páez Allende, F.: Semana méd. **48**:1273 (May 29) 1941.

Saba,[40] Semadeni,[18] Steffen,[41] Pitter,[42] Scherer,[43] Bailey,[44] Esterman,[13] Valdeavellano,[17] Nyquist and Vogt,[45] Groenouw and Severin,[46] Szekely,[47] Thorne,[29] Landesberg,[48] Lagrange and Laudat,[49] Heinonen,[28] Fänge,[50] Kolstad,[51] Berns,[52] Alvaro (clinical record) and Vasquez Barrière.

The myopia in the great majority of cases [33] was due to sulfanilamide, having been caused by sulfapyridine in only 3. Transient myopia caused by sulfanilamide varied from 1.50 to 4.50 D., with an average of 2.60 D., whereas the myopia caused by sulfapyridine was 7.00, 6.50 and 2.00 D., with an average of 5.25 D. The amount of reported myopia has generally been different for each eye, but differences are slight and always both eyes have been affected.

A slight majority of the patients with myopia have been men; 9.5 per cent (2 patients, both 18) were under 20, 38.1 per cent were between 20 and 30, 23.8 per cent were between 30 and 40 and 28.6 per cent were older than 40. Of the amounts of sulfanilamide taken before the onset of the myopic change in refraction, the smallest reported was 0.30 Gm. (Heinonen) and the largest 42 Gm. (Hornbogen). As to sulfapyridine, the smallest amount causing transient myopia was 5 Gm. and the largest 85 Gm.

Of the patients, 36.36 per cent had not taken more than 2.0 Gm. of the drug at the onset of the transient myopia; 13.6 per cent had taken between 2 and 4 Gm.; 13.7 per cent had taken between 4 and 10 Gm.; 22.6 per cent had taken from 10 to 20 Gm., and 13.7 per cent had taken more than 20 Gm. Of time elapsed between institution of use of sulf-

40. Saba, G.: Miopia transitoria da sulfamidici e sua genesi, Rassegna ital. d'ottal. **9**:708 (Nov.-Dec.) 1940.

41. Steffen, R.: Transitorische Myopie nach Behandlung mit Albuzid, Klin. Monatsbl. f. Augenh. **106**:597 (May) 1941.

42. Pitter, cited by Semadeni.[18]

43. Scherer, cited by Semadeni.[18]

44. Bailey, J.: Transitory Myopia Following Sulfanilamide Therapy, Am. J. Ophth. **24**:567 (May) 1941.

45. Nyquist, B., and Vogt, J. H.: Case of Transitory Myopia During Course of Catarrhal Fever and After Sulfanilamide Medication, Norsk mag. f. lægevidensk. **5**:100 (Jan. 20) 1940.

46. Groenouw and Severin: Akute transitorische Myopie nach Albucid, Deutsche med. Wchnschr. **67**:763 (July 11) 1941.

47. Szekely, J.: Transitory myopia, Gyógyászat **81**:172 (March 29) 1941.

48. Landesberg, J., in discussion on Bailey,[44] p. 568.

49. Lagrange, H., and Laudat, M.: Myopie spasmodique transitoire, accident de la médication organique soufrée, Bull. et mém. Soc. méd. d. hôp. de Paris **55**:883 (June 12) 1939.

50. Fänge, G.: Case of Transitory Myopia Developing After Therapy of Pneumonia with M & B 693, Svenska läk.-tidning. **36**:1197 (June 9) 1939.

51. Kolstad, A.: Transitory Myopia, Acta ophth. **19**:80, 1941.

52. Berns, cited by Kolstad.[51]

anilamide and onset of myopia, the minimum was twelve hours and the maximum fourteen days. With sulfapyridine the minimum time was fourteen days and the maximum thirty days (in the case in which 85 Gm. had been taken). The onset of the refractive defect occurred in the first twenty-four hours in 36.36 per cent of the cases; between the first and the fourth day in 13.6 per cent, between the fourth and the ninth day in 4.5 per cent, between the tenth and the twentieth day in 18.1 per cent (including a case in which use of the drug had been discontinued because of general signs of intolerance and then resumed) and after the twentieth day in 22.7 per cent (including several cases in which use of the drug had been discontinued because of some other reason than intolerance and then resumed). In 8 cases (22.22 per cent) the myopic change occurred after the administration of the drug had been discontinued and then resumed. In only 1 case had the administration of the drug been stopped because of the appearance of general signs of intolerance. In Spellberg's case, a man aged 41 had taken 1.94 Gm. of sulfanilamide and had then discontinued use of the drug for eight weeks, after which he ingested 0.10 Gm., this small amount being responsible for a myopia of 2.50 and 2.75 D., respectively, in the right and in the left eye. In another case (Rittenhouse) a man 34 years old had taken 4 Gm. of sulfanilamide in four days, stopped its use for another four and then resumed the same treatment. On the second day he had myopia of about 2.00 D. In another case (Kolstad) a woman 26 years old had taken 0.5 Gm. of sulfapyridine a day for one week, discontinued the treatment for three days and started it again by taking 1.5 Gm. daily. After the second tablet of 0.50 Gm. of sulfapyridine she complained of blurred vision, but she took the third tablet nevertheless, and the next morning she had 7.00 D. of myopia. In Lagrange and Laudat's case, a woman 32 years old took 1.5 Gm. of sulfanilamide daily for ten days without any ill effects. Use of the drug was stopped for fourteen days and then resumed. Six hours after taking a small amount the patient had myopia of 4.50 D. and showed general signs of intolerance. In Mattsson's 3 cases there is also mention of discontinuance and resumption of treatment. In 1 case there were symptoms of general intolerance which compelled the patient to discontinue use of the drug, and a resumption of treatment caused the appearance of transient myopia (Bristow). A woman 21 years old who had taken 4 Gm. of sulfanilamide a day for four days showed general symptoms of intolerance which compelled her to discontinue use of the drug. After twenty-three days she started taking 3.6 Gm. of azosulfamide and the next day had 2.5 D. of myopia and 0.5 D. of astigmatism.

The relation between the amount of drug taken and the degree of myopia is as follows: Patients who had taken up to 2.0 Gm. of a sulfonamide compound had an average of 2.00 D. of myopia. Patients

who had taken more than 2.0 Gm. and less than 10 Gm. had an average of 3.37 D. Patients who had taken more than 10 Gm. had an average of 3.31 D. The patients who discontinued use of the drug for some time and then resumed it are included in this group. When only patients who took the drug continuously are considered, the average of myopia in this group was 4.17 D.

The relation between the duration of the treatment and the degree of myopic change is as follows: The average of myopia appearing in patients who used a sulfonamide compound for twenty-four hours or less was 2.00 D.; more than one and less than five days, 3.16 D.; more than five and less than fifteen days, 4.60 D., and more than fifteen days, 6.50 D. All the patients in this group took the drug continuously.

The relation between the age of the patient and the degree of myopia is as follows: Patients under 20 had an average of 5.00 D. of myopia, those between 20 and 30 an average of 4.29 D., those between 30 and 40 an average of 2.58 D. and those past 40 an average of 2.40 D.

The shortest duration of myopia was one day and the longest fifteen days, with an average of four and nine-tenths days. There does not appear to be any relation between the amount of drug taken by the patient and the duration of the myopia.

Myopia generally disappears as soon as use of the drug is discontinued. Neither homatropine nor atropine succeeds in neutralizing the myopia as long as use of the sulfonamide compound is not discontinued (Posner [53]). After the alministration of the drug is discontinued, both atropine and homatropine seem to be able to help somewhat in bringing the refraction back to normal, although there does not appear to be a pronounced difference in recovery between the patients who had cycloplegics and those who did not.

Dr. Manoel A. Silva and I examined 14 patients for visual acuity, light and color sense, accommodation, muscle balance, state of the media and the fundi, ocular tension and pressure of the central artery of the retina before treatment was begun, for one reason or another, with sulfanilamide, sulfapyridine and sulfathiazole and after certain amounts of these drugs had been given. We made the following observations:

There were no changes in visual acuity, light and color perception, state of the media and the fundi, ocular tension and pressure of the central artery of the retina. In a case in which sulfathiazole had been given, an existing exophoria of 4 degrees was reduced to 2 degrees after the patient had taken 30 Gm. of the drug. A third examination revealed that the exophoria had been further reduced to 1 degree. In a case in which sulfapyridine had been given, an esophoria of 2 degrees was reduced to 1 degree. Accommodation, however, showed marked changes

53. Posner, A., in discussion on Bailey.[44]

in every case but 1. Thus, in 3 cases in which sulfanilamide had been taken there were the following results as measured with the cilometer: case 1, before treatment 7.00 D., after 10 Gm. of sulfacetimide 6.00 D. and a few days later, when the concentration in the blood was unchanged, 6.00 D.; case 2, before treatment 6.00 D. and after 10 Gm. of sulfacetimide 4.50 D.; case 3, before treatment 7.5 D., after 10 Gm. of sulfacetimide 6.00 D. and a few days later, when the concentration in the blood was unchanged, 6.00 D. In a group of 4 cases sulfanilamide was taken. The concentration in the blood at the second examination averaged 4 mg. per hundred cubic centimeters. Accommodation sank in 1 case from 8.00 to 6.00 D., in another from 6.50 to 6.00 D., in the third from 6.00 to 4.00 D. and in the fourth from 7.00 to 5.50 D. Of 2 cases in which sulfapyridine was taken (an average of 3 Gm. a day), there was a reduction from 6.50 to 6.00 D. in 1 and no change in the other. The second measurements were made when the concentration was 8 mg. per hundred cubic centimeters in the blood. In a group of 5 cases in which sulfathiazole was taken the accommodation was reduced from 6.00 to 4.00 D. in 1, from 6.50 to 4.00 D. in the second, from 5.00 to 4.00 D. in the third, from 7.50 to 6.00 D. in fourth and from 4.50 to 3.50 D. in the fifth. The concentration of the drug in the blood was measured in every case and showed an average of 4.5 mg. per hundred cubic centimeters; the second and third measurements showed approximately the same results.

To summarize, it may be stated that sulfonamide compounds given by mouth in the series of cases studied reduced accommodation from 0.50 to 2.50 D. as soon as the drug reached a certain concentration and kept it reduced. Sulfapyridine apparently caused the least reduction, but as only a few cases were observed it is not advisable to generalize.

In a series of 6 cases in which for some reason sodium sulfacetimide solution had to be used locally, and in which there was no corneal involvement capable of impairing sight considerably, the accommodation and the ocular tension were measured before treatment was begun and after 60 drops of a 15 per cent isotonic solution of sodium sulfacetimide had been instilled at five second intervals. No changes could be found either in accommodation or in ocular tension.

PATHOGENESIS

Edema of the lids can easily be explained as a localization on the skin of the lids of changes which occur frequently as a clinical toxic reaction to sulfonamide compounds (urticarial, angioneurotic, edematous, etc.), as rashes appearing in the course of therapy with sulfonamide compounds have been reported by several observers. The same explanation can be applied to the changes in the conjunctiva (conjunctivitis

and chemosis). Changes in the eyeball itself can be easily understood, too, when it is remembered that the sulfonamide drugs are absorbed in a high proportion by the cornea and that high concentrations have been found in the different parts of the eye. Thus the scleral reactions and possibly the changes in the aqueous (the presence of numerous circulating cells) and even in the iris (iritis) could be an expression of tissular reaction to high concentrations of a sulfonamide compound. Mydriasis could be explained by the action of the drug on the neural elements connected with the contraction of the sphincter. The only cataract occurred in a patient with iritis, and possibly the opacification of the lens was not caused by the sulfonamide drug at all. Retinal edema and optic neuritis are ocular repercussions similar to peripheral or central neuritis, which have often been found as toxic effects of therapy with sulfonamide compounds. Changes in the visual fields would be an expression of these changes. As to the narrowing of angioscotomas, this cannot be attributed to anoxia, as angioscotomas generally widen under that condition, and Rosenthal in his experiments administered oxygen to 1 of his patients during the experiment without noticing any change. According to Rosenthal, possibly there is a specific influence of sulfanilamide directly or indirectly on the synapse and on the nutrition of the retina. Retinal hemorrhages, as emphasized by Goar, can be compared to other hemorrhages which occur during use of sulfonamide compounds, such as petechiae in the skin and hemorrhages from the urinary and gastrointestinal tracts. Hypermetropia due to a sulfonamide compound has been mentioned only once. The explanation for this change might be found in refractive changes in the lens (loss of water or reduced concentration of salts) or in changes in accommodation. In Thorne's case there is no mention of a cycloplegic test, and possibly the manifest hyperopia of + 3.50 D. had always existed in a latent stage and was brought to notice through reduced accommodation. Astigmatism, which is almost always mentioned in cases of transient myopia, can be explained by changes in the crystalline lens. About these conditions more will be said presently.

Myopia is by far the most common ocular change due to therapeutic use of sulfonamide compounds. According to Missiroli, Brito, Pimentel, Saba and Valdeavellano, transient myopia is due to a spasm of accommodation. This view is not shared by the majority of authorities, however. Thus, Mattsson excluded spasm of accommodation because cycloplegics are not able to restore normal refraction. He stated the belief that changes in the structure of the lens are responsible for the myopia. In 1 of Mattsson's cases and in Scherer's case, the myopia plus the margin of accommodation the patient still had were above the total accommodation for the patient's age. Blankstein, discussing the matter extensively, suggested either the possibility of an allergic edema of the ciliary body or of the lens itself, or an imbalance of the osmotic

tension between the lens and the aqueous, leading to imbibition of water in the lens. According to Krause,[54] possibly a low p_H (sulfonamide compounds often cause acidosis) activates the osmotic power of the lens tissue, thus favoring its swelling. Blankstein ruled out spasm of accommodation because miosis, nausea, headache and other symptoms were not observed. Hornbogen emphasized the fact that the presence of astigmatism, which is so frequently associated with transient myopia, speaks in favor of changes in the lens structure. Bristow explained transient myopia as a sign of sensitization of the lens and excluded spasm of accommodation because cycloplegics do not seem to have any effect. This view has been shared by Bailey, Fänge and others. Rittenhouse also favored the sensitization hypothesis. According to him, rapid absorption of the drug causes changes in the sodium chloride metabolism, and this is then instrumental in altering the structure of the lens. Saba accepted the old view of a possible increase in the refractive index of the media due to the presence of the drug dissolved therein. Semadeni, in view of his case, in which a small amount of sulfanilamide taken for the first time was able to provoke transient myopia, did not favor the anaphylactic hypothesis but stated the belief that there may be a natural hypersensitivity. The fact that so little drug had been taken does not encourage acceptance of the hypothesis of absorption of the drug by the lens. Bailey emphasized the importance of the relative refraction of nucleus and cortex, any change in that relation causing alterations in the total refractive power of the lens.

Transient myopia is found in association with several conditions (alkalosis due to diet in peptic ulcer, nephritis, diarrhea, icterus, influenza, severe emaciation in tuberculosis, etc.) and is one of the toxic effects of arsphenamine. In cases of diarrhea associated with severe dehydration (Schieck,[55] Terrien,[56] Schläpfer [57]), the disturbance in the water-salt equilibrium may easily explain the changes in the lens. As to the action of arsphenamine, Milian and Perin [58] and Levy and Redslob [59] stated the belief that it is due to a spasm of accommodation. Atropine does not seem to affect transient myopia due to diarrhea or to diabetes. In 1 of Missiroli's cases, believing myopia to be due to a spasm of accommodation, he tried to overcome the contraction of

54. Krause, cited by Blankstein.[36]

55. Schieck, F.: Klin. Monatsbl. f. Augenh. **45**:40, 1907.

56. Terrien, F.: Les petits signes oculaires du diabète, Paris méd. **11**:312 (Oct. 22) 1921.

57. Schläpfer, H.: Ein Fall von akuter transitorischer Myopie, Klin. Monatsbl. f. Augenh. **100**:134, 1938.

58. Milian, G., and Perin: Paralysie arsénobenzolique de l'accommodation, Paris méd. **41**:388 (Nov. 12) 1921.

59. Levy, G., and Redslob, E.: Bull. Soc. franç. de dermat. et syph. **36**:483 (June) 1929.

the ciliary muscle with cycloplegics. Homatropine was tried with no avail. Then atropine was instilled in one eye; eighteen hours later the myopia had disappeared entirely from that eye, whereas the other eye had improved only by 0.25 D. In my own case and in Fänge's case, however, atropine did not seem to have the same effect, and only after three days did the myopic change subside completely.

Myopia appearing in association with diabetes has been extensively studied, and several theories have been established to explain it. Thus, it has been established beyond possible doubt that the changes occur in the lens and that no changes can be found in the radius of the cornea, in the anteroposterior axis of the eyeball, in the refractive index of the aqueous and of the vitreous or in the position of the lens. In patients with one aphakic eye, the myopic changes of diabetes have appeared only in the eye with a crystalline lens. Duke-Elder [60] expressed belief in a close relation between the lenticular changes and the concentration of dextrose in the blood and in the aqueous. Rönne [61] noticed that the changes in the lens occur quickly, appearing in a few moments, lasting for some weeks and then suddenly disappearing, and this observation led him to believe that the chemical changes cause an alteration in the tension of the lens fibers, which in their turn may determine relative changes in position of the cortex and the nucleus. This process was called by Rönne [61] "negative intracapsular accommodation." Granstroem said that he agreed with the view that probably no changes occur in the exterior form of the lens. According to Hudelo's ideas, accommodation has two components in the ciliary muscle, one which acts on the sphincter of the iris and another which acts on the tensor of the choroid. An overaction of the former causes a slight hyperopia, whereas an overaction of the latter causes a medium myopia. A lesion of both components will cause changes in accommodation. These several theories have been adopted to explain the pathogenesis of transient myopia due to sulfonamide compounds (Friedman and others).

COMMENT

The fact that sulfonamide compounds penetrate into the tissues of the eye in concentrations only somewhat lower than the concentration in the blood, and the demonstration of the potential absorption by the several parts of the eyeball, make it easy to understand why there is a comparatively large group of ocular changes which have been attributed to these drugs. One is even led to think that possibly many more ocular changes occur or have occurred without being noticed.

60. Duke-Elder, W. S.: Changes in Refraction in Diabetes Mellitus, Brit. J. Ophth. **9**:167 (April) 1925.

61. Rönne, H.: Zur pathologischen Anatomie der diabetischen Intoxikationsamblyopie, Arch. f. Ophth. **85**:489, 1913.

Experiments being excepted, the ocular changes which have been mentioned in the literature have only circumstantial evidence of being toxic effects of therapy with sulfonamide compounds. Some of them, however, can be associated with known toxic effects, such as changes in the skin (edema of the lids, conjunctivitis and chemosis), hemorrhagic symptoms (retinal hemorrhages) or even changes in the nerves (optic neuritis) and in the angioscotomas (edema of the retina, changes in the visual fields). Some changes, such as iritis and cataract, cannot be fully accepted as caused by the drugs, the diseases against which

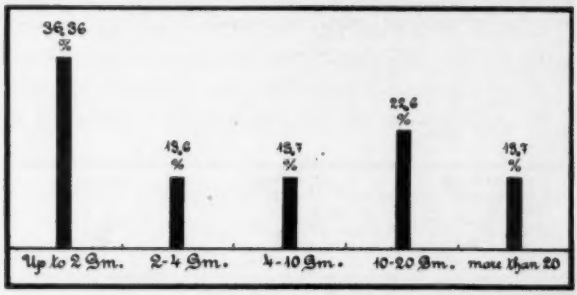

Chart 1.—Frequency of transient myopia according to the amount of sulfonamide compound taken before onset of the ocular change.

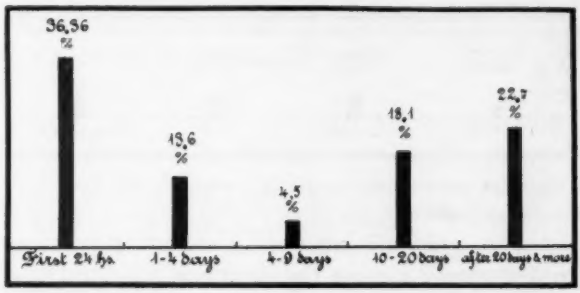

Chart 2.—Frequency of transient myopia according to the time elapsed between the beginning of therapy and onset of the ocular change.

the chemotherapy is established being themselves sometimes directly responsible for such changes.

By far the most common ocular complication due to sulfonamide compounds is transient myopia. Thirty-six well defined cases have come to my knowledge, and many more cases must have been observed which have never been reported. Still others would never have been noted, because the patient, owing to the ailment for which he took the drug, lay in bed, was depressed and did not notice his bad vision or, if he did, attributed it to his general condition. In other cases an existing latent hyperopia would mask a low degree of myopia.

Sulfanilamide and sulfapyridine are the only two sulfonamide compounds that appear to have caused transient myopia, sulfanilamide having caused it much the more often. Sulfathiazole has not been mentioned as the cause of transient myopia but has been responsible for conjunctivitis, retinal hemorrhages, etc. Sulfanilamide penetrates into the eye more than sulfapyridine, while sulfathiazole penetrates still less than the latter drug, this probably being the explanation. As to sulfadiazine, it has not been used long enough, probably for all its toxic effects to be observed.

The fact that small amounts of a sulfonamide compound can cause transient myopia in patients who never took the drug before, the fact that of 36 patients with transient myopia only 8 had used the drug for some time and had discontinued and then resumed the treatment, the fact that 36.36 per cent of all the patients had transient myopia after

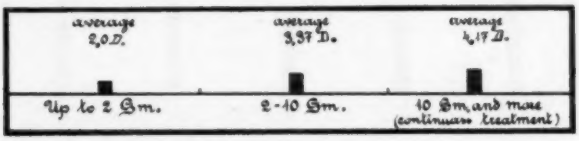

Chart 3.—Average amount of myopia according to the quantity of sulfonamide compound taken before onset of the ocular change.

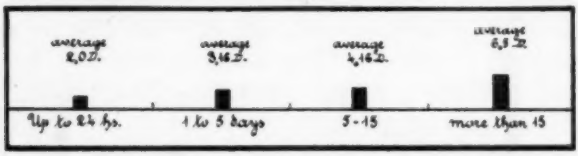

Chart 4.—Average amount of myopia according to the duration of treatment at onset of the ocular change.

having taken less than 2 Gm. of the drug and had used it for less than twenty-four hours, are all in favor of the discarding of anaphylaxis as the pathogenic mechanism. Some persons are apparently hypersensitive to the drug, and some 50 per cent of all those with transient myopia can be classified in that category, since half those reported on had taken only 4 Gm. or less of the drug and had been under treatment for a maximum of four days. On the other hand, about 40 per cent of the patients showed transient myopia only after the tenth day of treatment, and 36 per cent had taken more than 10 Gm. of the drug. These patients can be placed in the category of those having ordinary toxic effects which generally occur after the tenth day.

There appears to be a certain relation between the amount of a sulfonamide compound administered and the degree of transient myopia. Thus, with amounts of the drug up to 2 Gm. the myopia averages 2.00 D.,

whereas it averages 3.37 D. with doses up to 10 Gm. and 4.17 D. with amounts above 10 Gm. The length of time the drug is administered appears to have a certain influence on the degree of transient myopia. Thus, when the drug was given twenty-four hours or less the myopia averaged 2.00 D., whereas with longer periods of treatment the average was higher, reaching 6.50 D. when administration of the drug lasted more than fifteen days. The age of the patient, too, appears to have a certain relation to the degree of the myopia. With patients under 20 the average was 5.00 D.; with those between 20 and 30, 4.29 D.; with those between 30 and 40, 2.58 D., and with those over 40, 2.40 D. It should be emphasized, however, that although there does not seem to be any discrepancy in the results and that the numbers from which the averages were calculated were more or less homogeneous, the fact remains that only 36 cases were considered, and this number is small as a basis of generalizations.

Views about the pathogenesis of transient myopia in general are varied, and the same divergence of opinion prevails with regard to

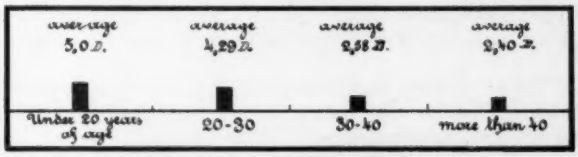

Chart 5.—Average amount of myopia according to age.

transient myopia due to the toxic effects of sulfonamide compounds. About one fact, however, there is no dispute. Transient myopia disappears of its own accord, in a comparatively short time, as soon as the use of the drug is discontinued. Missiroli, using atropine, was able to overcome myopia in one eye in eighteen hours, while the other eye, under the influence of homatropine, did not come back to normal as quickly, a fact which seems to speak in favor of spasm of the accommodation. In Fänge's case and in my case, atropine did not seem to have any effect. Moreover, as Mattsson and Kolstad pointed out, in some cases, at least, the degree of myopia was such that, added to the still existing accommodative power of the eye, it was far superior to the total accommodative power of any one of the patient's age. As Blankstein pointed out, in no case of transient myopia due to a sulfonamide compound have the other signs of spasm of accommodation, namely, nausea, headache and miosis, been mentioned. It is possible that several mechanisms occur, and perhaps a more careful study of each case will make possible the gathering of more knowledge in the future.

SUMMARY

The distribution of sulfonamide compounds in the eyes when these drugs are administered by mouth or parenterally or applied locally in the cul-de-sac or subconjunctivally is discussed according to the findings in the current literature and to some of my experiments.

The several changes in the eye mentioned as toxic effects of sulfonamide compounds are (1) palpebral edema, (2) conjunctivitis, (3) chemosis, (4) scleral reaction, (5) numerous cells in the aqueous and iritis, (6) mydriasis, (7) cataract, (8) changes in the angioscotomas, (9) edema of the retina, (10) reduction of the visual fields, (11) retinal hemorrhages, (12) optic neuritis, (13) undefined or unidentified blurred vision, (14) transient hyperopia, astigmatism or myopia and (15) changes in accommodation and heterophorias. Of these changes, transient myopia and the changes in accommodation seem to be the most frequent. Thirty-six cases of transient myopia came to my knowledge, and in my clinical experiments with patients who had to be treated with sulfonamide compounds I found reduced accommodation constantly.

The several pathogenic explanations for ocular changes due to the toxic effects of sulfonamide compounds are mentioned and discussed.

Prof. Q. Mingoja assisted in determining the amount of sulfacetimide in the aqueous of rabbits, and Dr. Galvanese Amato made possible the examination of patients taking sulfonamide compounds.

Clinical Notes

METAL EYE PROTECTOR

ARNO E. TOWN, M.D., NEW YORK

Various protective spectacles and glasses have been devised. The illustrated metal eye protector is valuable for military purposes, especially for ski troops, and has been adopted by the Russian government. It is made of stainless steel or cold roll and is a protection from sun, wind, sand and projectiles.

The protector consists of metal eyecups with cross stenopeic slits held together by a cross bar, which can be adjusted to regulate the

Metal eye protector.

interpupillary distance. The periphery of the cups is surrounded by soft rubber, which fits closely around the eyes. An elastic headband holds the device in place.

The advantages are as follows:

1. The protector is indestructible and light, weighing less than 5 ounces (150 Gm.).

2. Available daylight is 16 per cent; therefore, the protector can be used for glaring sun or blinding snow and yet give the necessary visibility.

3. It will not fog or steam as glass will.

4. It offers an added protection against injuries to the eyes without danger of breakage.

5. The device can be folded and carried in the pocket.

The metal eye protector is not intended for use in welding, aviation or reading.

It is constructed by the Iopak Corporation, 80 Broad Street, New York.

140 East Fifty-Fourth Street.

SIMPLE PROCEDURE FOR RELIEF OF ENTROPION

ALFRED WIENER, M.D., NEW YORK

The reluctance patients have for operative procedures, especially when the promise for relief is meager, has prompted me to report a simple procedure for an annoying condition known as entropion. Operation does not give satisfactory results, and often the disfigurement is disturbing to the patient. That a correction must be made of the disturbance every ophthalmologist knows. Besides the annoying symptoms which accompany it, there are the serious complications which may attend it, especially epiphora, erosion of the cornea and ulcers, with their consequences, which may prove fatal to the eye.

Recently I had a patient, an elderly man, who had severe conjunctivitis followed by entropion. All recognized nonoperative procedures were carried out but were of no avail. Operation was refused. I finally conceived the idea of having a spectacle frame made with a small attachment to the lower rim so adapted that slight pressure was exerted on the lower lid, everting it. This device does not annoy the patient and can hardly be seen. It has been worn for a month and has proved most satisfactory. I believe that if it is worn continuously for some time the spasm will be relieved. The patient is an eminent physician, and his enthusiastic remarks persuaded me to report this simple contrivance.[1]

1. It can be seen and procured at E. B. Meyrowitz, Inc., Fifth Avenue and Fifty-Seventh Street.

Ophthalmologic Reviews

EDITED BY DR. FRANCIS HEED ADLER

VIRUSES AND VIRUS DISEASES OF EYE

II. VIRUSES OF OCULAR IMPORTANCE

MAJOR PHILLIPS THYGESON

MEDICAL CORPS, ARMY OF THE UNITED STATES

(Concluded from Page 300)

LYMPHOGRANULOMA VENEREUM

In 1913 Durand, Nicolas and Favre [116] published the first comprehensive description of lymphogranuloma venereum, which had previously been confused with tuberculosis, syphilis and other diseases. In 1925 Frei [117] described the intradermal test which bears his name, in which an antigen prepared by sterilizing pus from unruptured buboes of lymphogranuloma venereum produces in persons who have or who have had the disease a specific inflammatory reaction. In 1930 Hellerström and Wassen [118] demonstrated that the causal agent is a filtrable virus.

Lymphogranuloma venereum, also known as lymphogranuloma inguinale or lymphopathia venerea(um), is primarily a disease of the lymphatic system. In the male the principal lesion is inguinal adenitis; in the female the characteristic lesions are elephantiasis of the external genitalia and chronic ulceration of the vulva, peritoneum, anus or rectum, leading to fistula and rectal stricture. A large number of extragenital manifestations have been described. Among these a number of ocular lesions,[119] especially a conjunctivitis with preauricular

Read in part before the Pacific Coast Oto-Ophthalmological Society, Portland, Ore., May 13, 1942.

116. Durand, M.; Nicolas, J., and Favre, M.: Lymphogranulomatose inguinale subaiguë d'origine génitale probable, peut-être vénérienne, Bull. et mém. Soc. méd. d. hôp. de Paris **35**:274, 1913.

117. Frei, W.: Eine neue Hautreaktion bei Lymphogranuloma inguinale, Klin. Wchnschr. **4**:2148, 1925.

118. Hellerström, S., and Wassen, E.: Étude du virus de la lymphogranulomatose inguinale (maladie de Nicolas-Favre), Compt. rend. Soc. de biol. **106**:802, 1931.

119. Macnie, J. P.: Ocular Lymphogranuloma Venereum, Arch. Ophth. **25**:255 (Feb.) 1941. von Haam, E., and Hartwell, R.: Experimental Conjunctivitis Caused by Virus of Lymphogranuloma Inguinale, J. Trop. Med. **34**:758, 1936. Benedek, T., and Olkon, D. B.: Lymphogranuloma Venereum as a Systemic Disease: Report of a Case with Involvement of the Skin and the Eye, Am. J. Syph., Gonor. & Ven. Dis. **25**:28, 1941. Oliphant, J. W.; Powell, W. F., and

(Footnote continued on next page)

adenopathy simulating Parinaud's conjunctivitis,[120] have been reported. The conjunctivitis occurs as a primary manifestation of the disease, and the first reported attack was an accidental laboratory infection with the virus. Ocular lesions reported as occurring secondarily to the genital disease have included optic neuritis, uveitis, keratitis and episcleritis. Beyond doubt the virus must now be included among the agents producing the so-called oculoglandular syndrome of Parinaud.

The virus filters well through Chamberland L2 and L3, Berkefeld V and N and Seitz EK filters, and it has been estimated, by means of filtration through gradocol membranes, that its particle size lies between 125 and 175 millimicrons (Broom and Findlay,[121] 1936) or between 100 and 140 millimicrons (Levaditi and co-workers,[122] 1936). It has been grown in tissue culture and on the chorioallantoic membrane of the developing chick embryo. Elementary bodies, like those in other virus diseases, have been reported by Miyagawa and associates,[123] and Findlay, MacKenzie and MacCallum[124] have described the existence of a developmental cycle with large and small forms comparable to that of psittacosis and inclusion conjunctivitis. A wide variety of experimental animals are susceptible, including monkeys, mice, rats, guinea pigs, dogs, cats, squirrels, marmots and sheep, but mice and guinea pigs have been used most extensively. The virus can be preserved in infected material at 4 C. for at least three weeks but does not survive over twenty-four hours at room temperature and perishes within ten minutes at 56 C.

The Frei test, which is a test for an allergic reaction comparable to the tuberculin test, gives positive results in a high percentage of cases, and false positive reactions are almost unknown. Its value in diagnosis

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Perrin, L. L.: Sulfadiazine in Lymphogranuloma Venereum Ophthalmitis, J. A. M. A. **118**:973 (March 21) 1942. Meyer, G. P., and Reber, J.: A Case of Corneal Ulcer Associated with Lymphogranuloma Venereum, Am. J. Ophth. **24**:161, 1941.

120. (*a*) Bollack, J.; Basch, G., and Desvignes, P.: Infection conjonctivale avec adénopathie due au virus de la maladie de Nicolas-Favre, Bull. Soc. d'opht. de Paris, 1936, p. 409. (*b*) Curth, W.; Curth, H. O., and Sanders, M.: Chronic Conjunctivitis Due to the Virus of Venereal Lymphogranuloma, J. A. M. A. **115**:445 (Aug. 10) 1940.

121. Broom, J. C., and Findlay, G. M.: Experiments on the Filtration of Climatic Bubo (Lymphogranuloma Inguinale) Virus Through "Gradocol" Membranes, Brit. J. Exper. Path. **17**:135, 1936.

122. Levaditi, C.; Parc, M.; Krassnoff, D., and Voet, J.: Ultrafiltration et dimensions approximatives du virus de la maladie de Nicolas et Favre, Compt. rend. Soc. de biol. **123**:1048, 1936.

123. Miyagawa, Y.; Mitamura, T.; Yaoi, H.; Isii, N., and Okanishi, J.: Studies on the Virus of Lymphogranuloma Inguinale, Jap. J. Exper. Med. **13**:1, 1935.

124. Findlay, G. M.; MacKenzie, R. D., and MacCallum, F. O.: A Morphological Study of the Virus of Lymphogranuloma Inguinale, Tr. Roy. Soc. Trop. Med. & Hyg. **32**:183, 1938.

is therefore extremely great, but unfortunately it is not always possible to obtain a suitable antigen. The antigen has also been used with some reported success in treatment, but use of sulfanilamide or a derivative will probably prove to be the treatment of choice. The primary ocular infection which I have observed (reported on by Curth, Curth and Sanders [120b]) healed rapidly and completely with sulfanilamide. This sensitivity of the virus to sulfanilamide is of considerable theoretic interest, since none of the typical viruses has proved to be susceptible to the drug. As will be discussed later, however, the viruses of trachoma and inclusion conjunctivitis, which have certain of the properties of the Rickettsiae, are strikingly sensitive to sulfanilamide. Both these viruses have developmental cycles with large and small forms, and the reported occurrence of a developmental cycle for the virus of lymphogranuloma venereum would appear to set it apart also from the typical viruses.

TRACHOMA AND INCLUSION CONJUNCTIVITIS

Trachoma.—In 1907 Halberstaedter and von Prowazek [125] described the occurrence in trachoma of cytoplasmic inclusion bodies in conjunctival epithelial cells. The inclusions were heterogeneous compositions of minute elementary bodies and, as later shown by Lindner,[126] of larger, more basophilic, often bipolar-staining coccobacillus-shaped bodies called initial bodies. These bodies were advanced as the causal agent of the disease. In 1912 Nicolle, Cuénod and Blaizot [127] reported that the agent of the disease was filtrable through Berkefeld V filters modified to minimize loss of the agent by adsorption. Their results were not confirmed until 1935, when Proctor and I [128] reported positive filtrations through gradocol membranes with an average pore diameter of 0.75 micron. Later Proctor, Richards and I [129] reported a positive result in a human volunteer with a gradocol membrane with an average pore diameter of 0.6 micron. Further confirmation of the filtrability of the agent of trachoma came from Julianelle and associates,[130] who

125. Halberstaedter, L., and von Prowazek, S.: Ueber Zelleinschlüsse parasitärer Natur beim Trachom, Arb. a. d. k. Gsndhtsamte **26**:44, 1907; Zur Aetiologie des Trachoms, Deutsche med. Wchnschr. **33**:1285, 1907.

126. Lindner, K.: Die freie Initialform der Prowazekschen Einschlusse, Arch. f. Ophth. **76**:559, 1910.

127. Nicolle, C.; Cuénod, A., and Blaizot, L.: Le magot animal réactif du trachome. Filtrabilité du virus. Pouvoir infectant des larmes, Compt. rend. Acad. d. sc. **155**:241, 1912. Nicolle, C.: État de nos connaissances d'ordre expérimental sur le trachome, Bull. Inst. Pasteur **19**:1, 1921.

128. Thygeson, P., and Proctor, F. I.: The Filtrability of Trachoma Virus, Arch. Ophth. **13**:1018 (June) 1935.

129. Thygeson, P.; Proctor, F. I., and Richards, P.: Etiologic Significance of the Elementary Body in Trachoma, Am. J. Ophth. **18**:811, 1935.

130. Julianelle, L. A.; Morris, M. C., and Harrison, R. W.: Studies on the Infectivity of Trachoma: Further Observations on the Filtrability of the Infectious Agent, Am. J. Ophth. **20**:890, 1937.

employed Berkefeld V filters, and from Stewart,[131] who used gradocol membranes.

Evidence indicating that this filtrable agent is indeed the elementary body of Halberstaedter and von Prowazek was provided by me[132] in 1933, when I showed that elementary bodies would pass gradocol membranes under conditions producing positive filtrations, and by Proctor, Richards and me[129] when we showed, in the filtration experiment on a human subject already mentioned, that elementary bodies were present in the material to be filtered, in the centrifuged part of the filtrate and in the eye of the subject with the experimental disease after onset of symptoms. Further evidence that the elementary bodies are the causal virus of trachoma was advanced by Wilson,[133] who demonstrated that the presence of epithelial cell inclusions, with their component elementary bodies, constitutes the earliest recognizable pathologic change in trachoma and can be demonstrated in 100 per cent of cases at onset. The constant occurrence of inclusions in trachoma at onset was confirmed by Richards and me.[134]

The claim of Busacca[135] and of Cuénod and Nataf[136] that the agent of trachoma should be classified with the Rickettsiae will be considered later.

Properties of Trachoma Virus.—Owing to the lack of a suitable and inexpensive susceptible animal, the properties of trachoma virus have not as yet been completely investigated. The particle size has not been determined by filtration through gradocol membranes, but on the basis of direct microscopic measurement of the elementary body (fig. 5) it would appear to be between 0.2 and 0.25 micron. The large form of the virus, the so-called initial body of Lindner, varies in size up to a micron or more in longest diameter. Unlike the elementary bodies of the typical large viruses, which require mordants or special stains for demonstration, the elementary bodies of trachoma stain well with Giemsa and similar dyes but stain faintly if at all with the ordinary bacterial stains. In staining properties they thus resemble the Rickettsiae.

131. Stewart, F. H.: Experimental Pathology of Trachoma, in Twelfth Annual Report of the Memorial Ophthalmic Laboratory, Giza, Cairo, Egypt, Schindler's Press, 1938, appendix no. 1, p. 1.

132. Thygeson, P.: The Nature of the Elementary and Initial Bodies of Trachoma, Arch. Ophth. **12**:307 (Sept.) 1934.

133. Wilson, R. P., in Eleventh Annual Report of the Memorial Ophthalmic Laboratory, Giza, Cairo, Egypt, Schindler's Press, 1937, p. 117.

134. Thygeson, P., and Richards, P.: Nature of the Filtrable Agent of Trachoma, Arch. Ophth. **20**:569 (Oct.) 1938.

135. Busacca, A.: Sulla presenza di germi semuli a Rickettsie nei tissuti trachomatosi, Klin. Monatsbl. f. Augenh. **91**:277, 1933.

136. Cuénod, A., and Nataf, R.: Deuxième note sur la présence d'éléments inframicrobiens dans les follicules trachomateux, Arch. d'opht. **52**:573, 1935.

The virus survives when tissues are ground and is sedimented by prolonged centrifugation at high speed. It does not resist drying. Successive freezing and thawing render infectious tissues inactive, but freezing alone appears to have no deleterious effect. Inactivation occurs at 37 C. within a few hours and at room temperature within twenty-four hours, but at 4 C. samples remain active for as long as a week. The death point was found by Julianelle[137] to be between 45 and 50 C. if maintained for fifteen minutes. According to Julianelle and associates,[138] glycerin has no preserving or deleterious effect on the virus. According to Stewart,[131] acid and alkali rapidly inactivate it. It is known to be

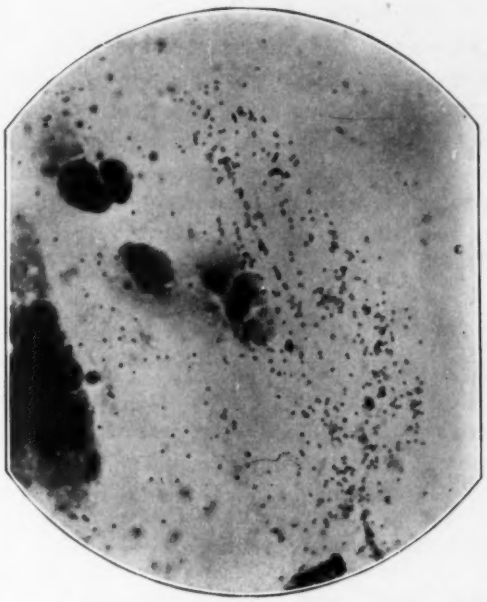

Fig. 5.—Elementary bodies of trachoma (Giemsa stain; magnification 1,500).

destroyed by bile and by various chemicals, including silver nitrate, cocaine, antimony and potassium tartrate, gentian violet and phenol.

Infection with trachoma in human beings or monkeys confers no permanent immunity. The virus has strict tissue localization and, although infective for monkeys and apes, produces a typical disease with pannus and scarring only in human beings. There is strict localization

137. Julianelle, L. A.: The Etiology of Trachoma, London, Commonwealth Fund, 1938, p. 179.

138. Julianelle, L. A.: On the Probable Nature of the Infectious Agent of Trachoma, Am. J. Path. **12**:775, 1936. Julianelle, L. A.; Harrison, R. W., and Morris, M. C.: The Probable Nature of the Infectious Agent of Trachoma, J. Exper. Med. **65**:735, 1937.

to the epithelium of the conjunctiva and cornea; subepithelial effects, such as cellular infiltration, necrosis and cicatrization, are secondary and caused no doubt by soluble products liberated in the epithelium. A recent report by Braley [139] indicates that the transitional epithelium at the external os of the cervix in baboons is also susceptible.

Trachoma virus, like the virus of inclusion conjunctivitis, has resisted all efforts at cultivation in tissue culture or in the yolk sac or chorioallantois of the developing chick embryo. The extreme fastidiousness of the virus is shown by its failure to grow in human conjunctival and corneal epithelium,[140] its normal host cells.

Trachoma is strikingly affected by sulfanilamide, as shown by the results of Loe [141] and others.

Inclusion Conjunctivitis.—This virus disease is seen most frequently as an acute papillary conjunctivitis of the newborn infant, but it occasionally affects adults, appearing usually as an acute or subacute follicular conjunctivitis but exceptionally as an acute papillary conjunctivitis. The disease has been known under a variety of names, including inclusion blennorrhea, paratrachoma and swimming pool conjunctivitis, the last-mentioned name being due to its occasional occurrence in epidemic form among swimmers.

Properties of Inclusion Conjunctivitis Virus.—The virus has been filtered through Berkefeld V filters by Gebb [142] and by Botteri,[143] through gradocol membranes by Thygeson [144] and by Tilden and Gifford [145] and, more recently, through Berkefeld V filters by Julianelle and Harrison.[146] It filters much more easily than trachoma virus, owing no doubt to its high concentration in the conjunctival tissues. The particle size has not been accurately measured by gradocol filters, but since the virus has

139. Braley, A. E.: Inclusion Blennorrhea, Am. J. Ophth. **21**:1203, 1938.

140. Thygeson, P.: Cultivation of Trachomatous Conjunctival Epithelium in Vitro, Arch. Ophth. **21**:229 (Feb.) 1939. Harrison, R. W., and Julianelle, L. A.: Studies on the Infectivity of Trachoma: VI. Cultivability of the Infectious Agent in Tissue Cultures, Am. J. Ophth. **20**:360, 1937.

141. Loe, F.: Sulfanilamide Treatment of Trachoma: Preliminary Report, J. A. M. A. **111**:1371 (Oct. 8) 1938.

142. Gebb, H.: Experimentelle Untersuchungen über die Beziehungen zwischen Einschlussblennorrhoe und Trachom, Ztschr. f. Augenh. **31**:475, 1914.

143. Botteri, A.: Klinische, experimentelle und mikroskopische studien über Trachom, Einschlussblennorrhöe und Frühjahrskatarrh, Klin. Monatsbl. f. Augenh. **50**:653, 1912.

144. Thygeson, P.: The Etiology of Inclusion Blennorrhea, Am. J. Ophth. **17**:1019, 1934.

145. Tilden, E. C., and Gifford, S. R.: Filtration Experiment with the Virus of Inclusion Blennorrhea, Arch. Ophth. **16**:51 (July) 1936.

146. Julianelle, L. A.; Harrison, R. W., and Lange, A. C.: Studies on Inclusion Blennorrhea: III. Experimental Considerations on the Etiology, Am. J. Ophth. **21**:1230, 1938.

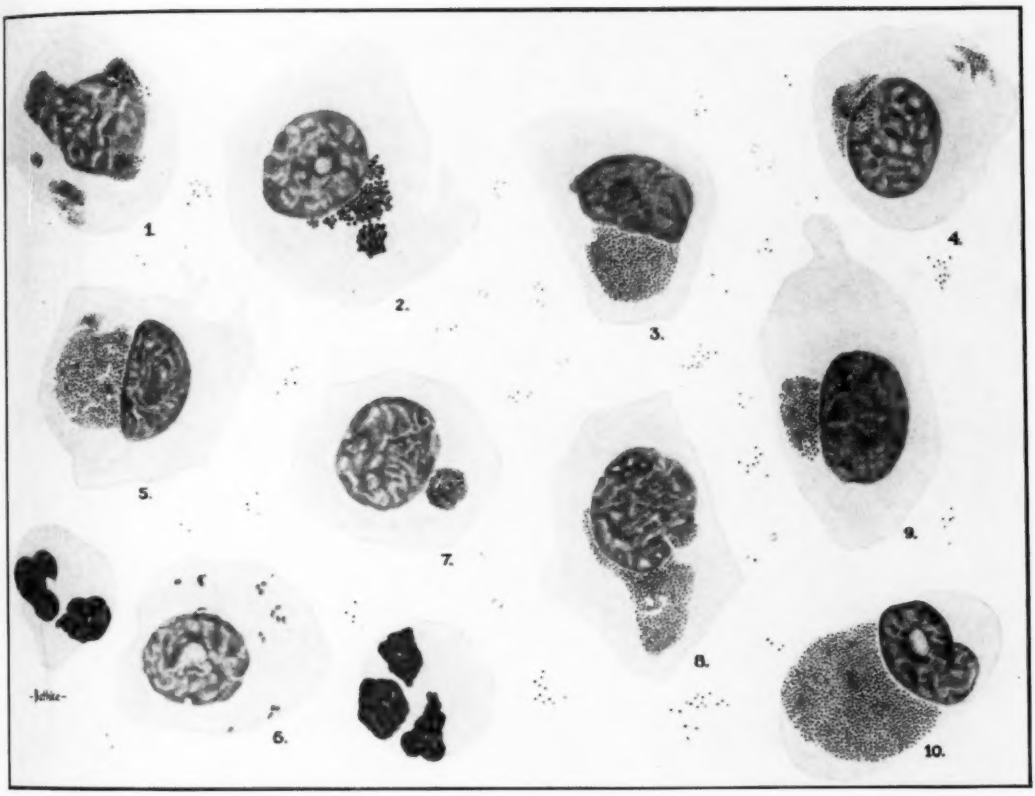

Fig. 6.—Inclusion bodies of inclusion conjunctivitis (Giemsa stain; magnification approximately 560).

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failed to pass filters [144] of 0.25 micron or less and has passed filters of 0.53 micron, the particle size must lie between 0.39 and 0.15 micron. Direct microscopic measurement of the elementary body shows it to be like the trachoma elementary body, from 0.2 to 0.25 micron in diameter, the initial body, or large form, being 1 micron and larger.

Like the virus of trachoma, inclusion conjunctivitis virus has a strict tissue localization, affecting only the conjunctival epithelium and the genital epithelium [147] (urethral in the male and cervical in the female) of human beings, monkeys and apes. As in trachoma, the virus has been demonstrated only in the epithelium, the subepithelial infiltration being a result of soluble toxic products liberated in the epithelium.

The virus forms inclusion bodies (fig. 6) which are morphologically indistinguishable from those of trachoma. They are cytoplasmic, basophilic and, like those of trachoma, have a carbohydrate matrix [148] which gives a glycogen stain with compound solution of iodine. The small inclusions, made up of initial bodies, stain blue with Giemsa stain, while the large inclusions, made up predominantly of elementary bodies, stain a bluish red. The virus, like the viruses of trachoma, psittacosis and lymphogranuloma venereum, undergoes a regular sequence of morphologic development from a small form to a large form and back to a small form, as indicated in figure 7. This developmental cycle is best studied during the incubation period of the experimental human disease; scrapings taken at different intervals after inoculation show the inclusions in different stages of maturity. The complete cycle from elementary body to elementary body seems to require almost forty-eight hours.

Like infection with trachoma, infection with inclusion conjunctivitis confers no permanent immunity. Baboons can be reinfected without difficulty after recovery from experimental inclusion conjunctivitis, and the reinfection can be repeated apparently indefinitely. There is no cutaneous allergy to the virus, and elementary body suspensions are not agglutinated by the serum of patients having or having had the disease. The occurrence of an ocular infection in a woman in whose newborn baby inclusion blennorrhea had just developed indicates that a genital infection does not confer ocular immunity.[144]

The virus of inclusion conjunctivitis is strikingly sensitive to sulfanilamide,[149] and the inclusion bodies disappear during the first three days

147. Lindner, K.: Zur Aetiologie der gonokokkenfreien Urethritis, Wien. klin. Wchnschr. **1**:284, 1910. Thygeson, P., and Mengert, W. F.: The Virus of Inclusion Conjunctivitis, Arch. Ophth. **15**:377 (March) 1936. Thygeson, P., and Stone, W., Jr.: The Epidemiology of Inclusion Conjunctivitis, ibid. **27**:91 (Jan.) 1942.

148. Rice, C. E.: The Carbohydrate Matrix of the Epithelial-Cell Inclusion in Trachoma, Am. J. Path. **14**:455, 1938.

149. Thygeson, P.: Treatment of Inclusion Conjunctivitis with Sulfanilamide, Arch. Ophth. **25**:217 (Feb.) 1941.

of treatment. Treatment must be continued six or seven days to effect permanent cure. The disease in the infant can be satisfactorily treated with sulfanilamide or, better, sulfathiazole in ointment form,[150] but adults usually require supplementary oral therapy.

Relation of Trachoma to Inclusion Conjunctivitis.—These two diseases resemble each other strikingly, not only in the morphologic identity of their inclusion bodies but in their clinical pictures. Similarities consist in (1) an incubation period of five to ten days, (2) sensitivity to

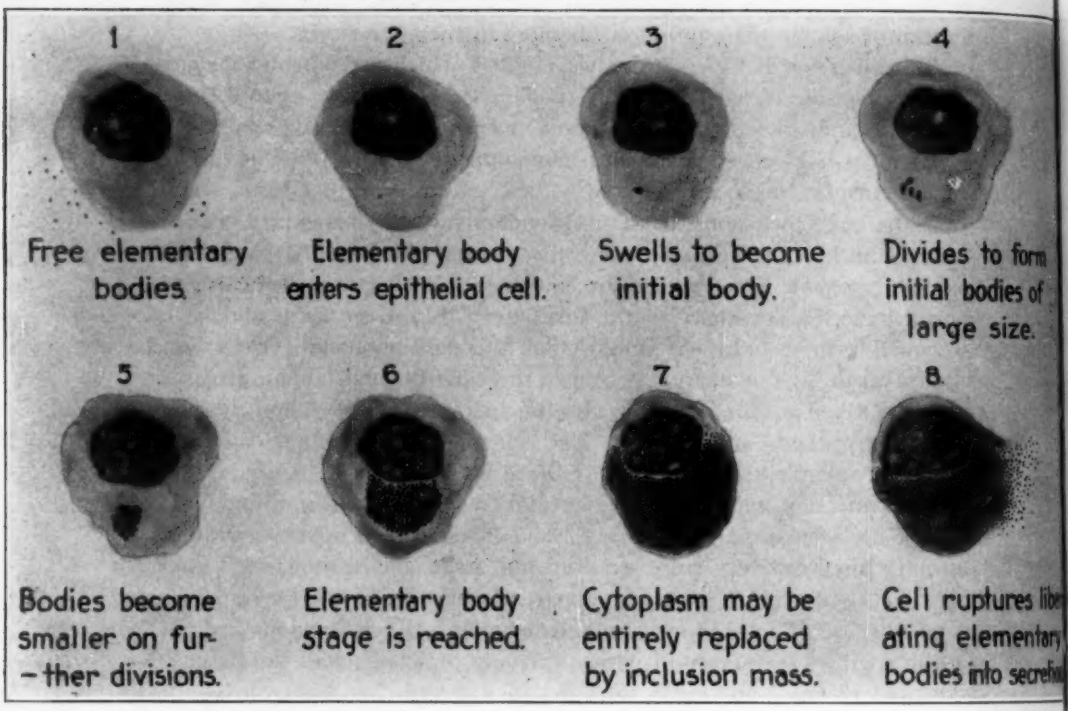

Fig. 7.—Developmental cycle of inclusion body of inclusion conjunctivitis.

sulfanilamide, (3) the picture of the experimental disease in monkeys and apes and (4) the occurrence of both follicular and papillary types of reaction. Trachoma differs from inclusion conjunctivitis principally in that it leads to pannus and cicatrization; this means that trachoma virus is capable of causing cell death in subepithelial tissues, while inclusion conjunctivitis virus is not. Experimental trachoma in baboons, while clinically similar, appears to last longer than experimental inclusion conjunctivitis. There is also the difference that in trachoma the pre-

150. Thygeson, P., and Stone, W., Jr.: The Treatment of Inclusion Conjunctivitis with Sulfathiazole Ointment, J. A. M. A. **119**:407 (May 30) 1942.

dominant involvement is in the upper fornices and tarsus and that in inclusion conjunctivitis it is in the lower fornices and tarsus. Trachoma rarely if ever occurs in full-blooded Negroes, while inclusion conjunctivitis, in my experience, has been more common in Negroes than in white persons and has occurred in what appeared to be pure Negroes. Although I have seen trachoma in Sudanese Negroes of mixed blood in Egypt and in West Indian Negroes of mixed blood, I have not seen the disease in American Negroes except in a young woman one quarter white in whom there developed an acute unilateral trachoma with pannus which healed rapidly with sulfanilamide.

The similarities of the two diseases, particularly the morphologic identity of the inclusions and their component elementary and initial bodies, early suggested (Lindner [151]) that the two viruses, like the viruses of variola and vaccinia, might be variants, the virus of inclusion conjunctivitis being the variant whose ocular pathogenicity had become reduced owing to long life in the genital mucosa. No proof for this hypothesis has as yet been advanced, although Braley [152] recently obtained infection of the cervix of baboons with trachoma virus, and it is thus conceivable that an experimental test of the hypothesis may eventually be made.

Rickettsia in Trachoma.—In 1933 Busacca [135] claimed the demonstration of Rickettsia-like organisms, which he sharply differentiated from the elementary and initial bodies, in the epithelium and in the subepithelial tissues of trachoma. In 1935 Cuénod and Nataf [136] described similar bodies, which they considered to be organisms of the Rickettsia group, although they identified them with the elementary and initial bodies. They described them as occurring in trachoma follicles, a location in which other observers have never found Prowazek bodies. After the appearance of these reports I [153] requested and received representative slides from both Busacca and Cuénod and Nataf but was unable to find Rickettsia-like bodies in the cells of the subepithelial infiltrates or in the follicles and came to the conclusion that the investigators were confusing cell granules, exaggerated by overstaining, with organisms of the Rickettsia group. I showed these slides to a number of investigators familiar with the Rickettsiae, and these observers arrived at the same conclusion. Furthermore, I have subjected trachomatous material of known infectivity to Rickettsia stains but have never been able to demonstrate any organism-like bodies except the elementary and initial bodies, and these have been limited entirely to the epithelium. Follicular con-

151. Lindner, K., in Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936, p. 442.

152. Braley, A. E.: Relation Between Virus of Trachoma and Inclusion Blennorrhea, Arch. Ophth. **22**:393 (Sept.) 1939.

153. Thygeson, P.: Problem of Rickettsias in Trachoma, Arch. Ophth. **20**:16 (July) 1938.

tents have always been organism free. Further evidence of the rickettsial nature of the agent of trachoma was claimed on the basis of the occurrence of positive Weil-Felix [154] reactions in patients with trachoma and on the basis of a louse transmission experiment.[155] It has since been shown [156] conclusively that the Weil-Felix reaction occurs no more frequently in the trachomatous than in the nontrachomatous patient, and the louse transmission experiment could not be repeated by Weigl,[157] de Rötth [158] or Braley.[159] It seems safe, therefore, to conclude that there are no Rickettsia-like bodies other than the Prowazek bodies in trachoma.

The claim of Foley and Parrot [160] that the elementary and initial bodies belong to the Rickettsia group, although based entirely on direct microscopic examination, would appear to be supported by certain evidence. In the first place, the elementary and initial bodies have certain of the staining properties of the Rickettsiae in that they stain with Giemsa and similar dyes more readily than do any of the typical virus elementary bodies; in the second place, the morphologic variation from initial body to elementary body which is seen in atypical viruses, such as the viruses of psittacosis,[161] inclusion blennorrhea [144] and lymphogranuloma venereum,[121] also occurs in such a rickettsial disease as heartwater in sheep, in which Rickettsia ruminantium [162] exhibits rather typical elementary and initial body forms. Against the rickettsial nature of the trachoma bodies is the absence of a proved arthropod vector, the

154. Derkac, V.: Zur Aetiologie des Trachoms, Klin. Monatsbl. f. Augenh. **99**:596, 1937; Zur Frage der Rickettsien bei Trachom, ibid. **101**:247, 1938.

155. Cuénod, A., and Nataf, R.: Nouvelles recherches sur le trachome: IV. Note: Recherches expérimentales, Arch. d'opht. **53**:355, 1936; Nouvelles recherches sur le trachome, Arch. Inst. Pasteur de Tunis **26**:1, 1937.

156. Bengtson, I. A.: The Question of the Rickettsial Nature of Trachoma, Am. J. Ophth. **23**:770, 1940. Julianelle, L. A., and Smith, J. E.: Studies on the Infectivity of Trachoma: IX. Rickettsial Concept, ibid. **23**:62, 1940. Kirk, R.; McKelvie, A. R., and Drysdale, A. D.: The Weil-Felix Reaction in Trachoma, J. Hyg. **39**:553, 1939.

157. Weigl, R.: Trachomstudium: I. Rickettsia Rocha-Limae (Weigl) ist nicht der Trachomerreger, Zentralbl. f. Bakt. (Abt. 1) **143**:291, 1939.

158. de Rötth, A.: The Problem of the Etiology of Trachoma: I. Rickettsiae, Arch. Ophth. **22**:533 (Oct.) 1939.

159. Braley, A. E.: The Rickettsia Question in Trachoma: II. The Louse as a Possible Disseminating Agent for the Virus, Arch. Ophth. **22**:262 (Aug.) 1939.

160. Foley, H., and Parrot, L.: Sur la Rickettsia du trachome, Compt. rend. Soc. de biol. **124**:230, 1937.

161. Bedson, S. P., and Bland, J. O. W.: A Morphological Study of Psittacosis Virus, with the Description of a Developmental Cycle, Brit. J. Exper. Path. **13**:461, 1932.

162. Jackson, C.: The Microscopic Diagnosis of Heartwater: A Preliminary Note on the Value of Intima Smears, Seventeenth Report of the Director of Veterinary Services and Animal Industry, Union of South Africa, August 1931, p. 161.

lack of significant Weil-Felix reactions and the occurrence in trachoma of a virus type of inclusion body containing a stainable carbohydrate matrix; although one of the Rickettsiae does form colonies resembling the trachoma inclusions, no stainable matrix has as yet been demonstrated for them. Furthermore, the typical Rickettsiae are characterized by their lack of filtrability, by the fact that they confer definite and permanent immunity and by their rather broad tissue activity, particularly with respect to tissues of mesodermal origin, such as the endothelium of blood vessels. It would seem, therefore, to be more logical to classify the agent of trachoma with the larger viruses, but it must be recognized that trachoma virus, together with the viruses of inclusion blennorrhea, psittacosis and lymphogranuloma venereum, forms a group of atypical viruses transitional between the typical large viruses and the Rickettsiae (fig. 8).

FOOT AND MOUTH DISEASE

This disease, while primarily a disease of cattle, occasionally spreads to human beings, and severe ocular complications have been reported. For example, Breiner [163] reported a case in which there were edema of the eyelids, conjunctivitis, preauricular adenopathy and a semiadherent membrane covering the margin of the upper lid. There was spontaneous recovery. Other cases have been reported by Illig [164] and by Ascher and Klauber [165] in which there was severe keratoconjunctivitis with pannus and phlyctenule-like nodules at the limbus which ultimately ulcerated. The virus is one of the smallest, having a particle size [166] estimated at from 8 to 12 millimicrons. It is not immunologically uniform, at least three distinct types, A, B and C, having been recognized (de Boerr [167]).

MUMPS

A number of ocular complications have been described as occurring in mumps. These have included optic neuritis,[168] keratitis [169] with ulceration and episcleritis, iridocyclitis, choroiditis, thrombosis of the

163. Breiner, A.: Foot and Mouth Disease Localized in the Eye, Am. J. Ophth. **20**:878, 1937.

164. Illig, H.: Aphthae epizooticae beim Menschen mit besonderer Berücksichtigung der Augensymptome, Arch. f. Augenh. **83**:64, 1918.

165. Ascher, K. W., and Klauber, E.: Bindehaut und Hornhauterkrankung bei Maul und Klauenseuche, Klin. Monatsbl. f. Augenh. **67**:396, 1921.

166. Galloway, I. A., and Elford, W. J.: Filtration of the Virus of Foot-and-Mouth Disease Through a New Series of Graded Collodion Membranes, Brit. J. Exper. Path. **12**:407, 1931.

167. de Boerr, E.: Investigations on Foot and Mouth Disease, Nederland, Indische blad. diergeneesk **53**:127, 1941.

168. Swab, C. M.: Encephalitic Optic Neuritis and Atrophy Due to Mumps, Arch. Ophth. **19**:926 (June) 1938. Cosserat, B.: Névrite optique ourlienne, Bull. Soc. d'opht. de Paris **51**:304, 1939.

169. Danielson, R. W., and Long, J. C.: Keratitis Due to Mumps, Am. J. Ophth. **24**:655, 1941.

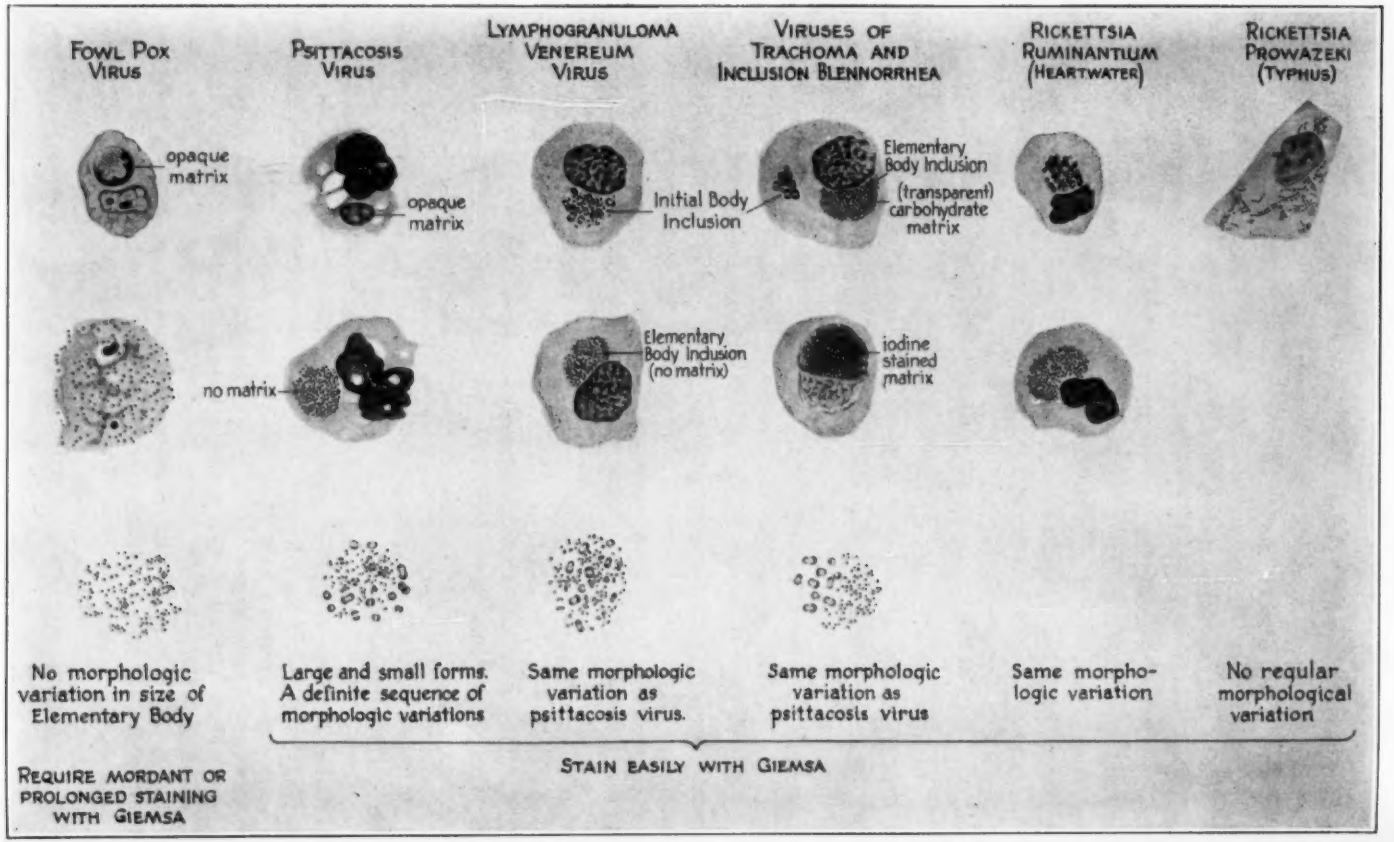
Fowl Pox Virus
Psittacosis Virus
Lymphogranuloma Venereum Virus
Viruses of Trachoma and Inclusion Blennorrhea
Rickettsia Ruminantium (Heartwater)
Rickettsia Prowazeki (Typhus)
opaque matrix
opaque matrix
Initial Body Inclusion
Elementary Body Inclusion
(transparent) carbohydrate matrix
no matrix
Elementary Body Inclusion (no matrix)
iodine stained matrix
No morphologic variation in size of Elementary Body
Large and small forms. A definite sequence of morphologic variations
Same morphologic variation as psittacosis virus.
Same morphologic variation as psittacosis virus
Same morphologic variation
No regular morphological variation
Require mordant or prolonged staining with Giemsa
Stain easily with Giemsa

Fig. 8.—Relationships between the large viruses and the Rickettsiae.

central retinal vein, paralysis of internal and external ocular muscles [170] and dacryoadenitis. The last-named complication may occur in as many as 20 per cent of cases (Bonnet [171]).

The particle size of the virus of mumps has not been determined, but it passes V and N Berkefeld filters [172] and does not pass Chamberland L2 filters.[173] Eosinophilic bodies measuring up to 4 microns have been found in the cytoplasm of acinar cells in the parotid (Johnson and Goodpasture [174]). A number of monkeys are susceptible to the virus [175] and chimpanzees somewhat more so. Positive transmission to rabbits and cats has been claimed. In human beings the virus produces a lasting immunity, but second attacks have been recorded. Convalescent serum has been used prophylactically with some success.[176]

DENGUE FEVER

Definite, if rare, ocular complications may occur in the course of dengue fever. Discomfort on movement of the eyes and tenderness on palpation are common, and ocular lesions in the form of ocular muscle paralyses, iridocyclitis and keratitis have been reported (van Rooyen and Rhodes [177]). The virus was first filtered by Ashburn and Craig [178] (1907) and its filtrability confirmed by Cleland, Bradley and MacDonald,[179] who passed the virus through the Pasteur-Chamberland F filter, and by numerous workers since then. The particle diameter of the virus is not known, but the ease with which it may be filtered suggests small size. Shortt, Rao and Swaminath [180] have claimed

170. Butler, T. H., and Wilson, A. J.: Ocular Paralysis Following Mumps, Brit. M. J. **1**:752, 1937.

171. Bonnet, P.: Les complications oculaires des oreillons, J. de méd. de Lyon **19**:171, 1938.

172. Johnson, C. D., and Goodpasture, E. W.: Investigation of Etiology of Mumps, J. Exper. Med. **59**:1, 1934.

173. Levaditi, C.; Martin, R.; Bonnefoi, A., and Schoen, R.: L'étiologie des oreillons, Compt. rend. Acad. d. sc. **201**:174, 1935.

174. Johnson, C. D., and Goodpasture, E. W.: Histopathology of Experimental Mumps in Monkey: Macacus Rhesus, Am. J. Path. **12**:495, 1936.

175. Levaditi, C.; Martin, R.; Bonnefoi, A., and Schoen, R.: L'étiologie des oreillons, Compt. rend. Acad. d. sc. **200**:594, 1935.

176. Regan, J. C.: Serum Prophylaxis of Epidemic Parotitis, J. A. M. A. **84**:279 (Jan. 24) 1925. Zeligs, M.: Convalescent Serum in Prevention of Mumps, J. Pediat. **1**:727, 1932.

177. van Rooyen and Rhodes,[77] p. 430.

178. Ashburn, P. M., and Craig, C. F.: Experimental Investigations Regarding the Etiology of Dengue Fever, with a General Consideration of the Disease, Philippine J. Sc. **2**:93, 1907; abstracted, J. Infect. Dis. **4**:440, 1907.

179. Cleland, J. B.; Bradley, B., and MacDonald, W.: Further Experiments in Etiology of Dengue Fever, J. Hyg. **18**:217, 1919.

180. Shortt, H. E.; Rao, R. S., and Swaminath, C. S.: Cultivation of Viruses of Sandfly Fever and Dengue Fever on Chorio-Allantoic Membrane of Chick-Embryo, Indian J. M. Research **23**:865, 1936.

cultivation of the virus on the chorioallantoic membrane of the developing egg. The disease is known to be transmitted by the mosquitoes Aedes aegypti, Aedes albopictus and others. Transmission is not ordinarily a simple mechanical process, since an incubation period of six days seems to be required before the insects become capable of infecting man. The virus produces an immunity lasting from one to seven years; no effective vaccine has as yet been developed. None of the ordinary laboratory animals is completely susceptible to the virus, though some may harbor it for considerable periods after inoculation without obvious clinical disease. Simmons and associates [181] found that the Japanese monkey Macacus fuscatus showed a transient febrile illness after experimental inoculation.

SANDFLY FEVER (PAPPATACI FEVER)

Ocular lesions, including conjunctivitis and, more rarely, neuroretinitis, have been recorded by Jayle and Mastier [182] (1935) and by Rameev [183] (1936) as complicating sandfly fever. The bulbar conjunctiva may undergo extensive congestion. The virus was first filtered by Doerr [184] in 1908, and confirmation came from Tedeschi and Napolitani,[185] Graham,[186] Kligler and Aschner [187] and Shortt, Poole and Stephens.[188] According to the filtration experiments of Shortt, Pandit and Rao,[189] who found the virus to be retained by gradocol membranes of 0.38 micron average pore diameter and smaller, it must be relatively large. These workers cultivated the virus on the chorioallantois and also in tissue cultures of minced chick embryo in Tyrode's solution. Of the laboratory animals inoculated, only monkeys (Macacus cynomolgus and

181. Simmons, J. S.; St. John, J. H., and Reynolds, F. H. K.: Experimental Studies of Dengue, Philippine J. Sc. **44**:1, 1931.

182. Jayle, G. E., and Mastier, P.: Symptômes et complications oculaires de la fièvre boutonneuse, Bull. et mém. Soc. franç. d'opht. **48**:273, 1935.

183. Rameev, R. S.: Ocular Complications of Pappataci Fever, Sovet. vestnik oftal. **9**:347, 1936; cited by van Rooyen and Rhodes,[77] p. 509.

184. Doerr, R.: Ueber ein neues invisibles Virus (Epidemisches Sommerfieber, sogenannte Hundskrankheit), Vorläufige Mitteilung, Berl. klin. Wchnschr. **45**:1847, 1908.

185. Tedeschi, A., and Napolitani, M.: Experimentelle Untersuchungen über die Aetiologie des Sommerfiebers, Centralbl. f. Bakt. (Abt. 1) **57**:208, 1910-1911; **61**:502, 1911.

186. Graham, G. F.: Sandfly Fever in Chitral (N. India), Brit. M. J. **2**:169, 1915.

187. Kligler, I. J., and Aschner, M.: Studies on Etiology of Phlebotomus and Dengue Fever: Is Leptospira the Causative Virus? Ann. Trop. Med. **22**:151, 1928.

188. Shortt, H. E.; Poole, L. T., and Stephens, E. D.: Sandfly Fever on Indian Frontier: Preliminary Note on Some Laboratory Investigations, Indian J. M. Research **21**:775, 1934.

189. Shortt, H. E.; Pandit, C. G., and Rao, R. S.: Virus of Sandfly Fever in Culture and Certain of Its Properties, Indian J. M. Research **26**:229, 1938.

Macacus rhesus) appear to be susceptible to infection and they only mildly so. The virus induces an immunity which is incomplete, and repeated attacks are not unusual. As indicated by its name, the virus is transmitted by the sandfly Phlebotomus pappatacii and probably others.

LOUPING ILL

Louping ill is a virus disease of sheep which under natural conditions is not transferred to human beings. A number of infections, however, have occurred among laboratory workers. Rivers and Schwentker [190] reported 4 cases; among other nervous manifestations diplopia was noted, and in 1 case a retrobulbar neuritis developed. The virus is one of the small ones (15 to 20 millimicrons) [191] and is transmissible to pigs, mice, monkeys and rats. It has been grown in tissue culture [192] and has produced transmissible lesions on the chorioallantois of the developing egg.[193] After infection animals are usually immune to reinfection.[194]

OTHER VIRUS DISEASES WITH OCCASIONAL OCULAR MANIFESTATIONS

Diplopia and ocular muscle pareses or paralyses are occasional complications of certain other virus diseases. These include equine encephalomyelitis, poliomyelitis, lymphocytic choriomeningitis, Australian X disease, St. Louis encephalitis, rabies and, especially, encephalitis lethargica. The virus nature of the last-mentioned disease, however, is still in doubt. Benign optic neuritis occurs rarely in influenza (Robitashvili [195]), and iridocyclitis [196] and interstitial keratitis [197] have also been reported. It is of interest that Burnet, Jackson and Robertson [198] have reported on the intraocular inoculation of monkeys with

190. Rivers, T. M., and Schwentker, F. F.: Louping-Ill in Man, Proc. Soc. Exper. Biol. & Med. **30**:1302, 1933; J. Exper. Med. **59**:669, 1934.

191. Elford, W. J., and Galloway, I. A.: Size of Virus of Louping-Ill of Sheep by Method of Ultrafiltration Analysis, J. Path. & Bact. **37**:381, 1933.

192. Rivers, T. M., and Ward, S. M.: Cultivation of Louping-Ill Virus, Proc. Soc. Exper. Biol. & Med. **30**:1300, 1933.

193. Burnet, F. M.: Observations on Effect of Louping-Ill Virus on Developing Egg, J. Path. & Bact. **17**:294, 1936.

194. Burnet, F. M.: Inapparent Infection of Rat with Louping-Ill Virus, J. Path. & Bact. **42**:213, 1936.

195. Robitashvili, K. F.: Involvement of the Optic Nerve in Influenza, Sovet. vestnik oftal. **15**:79, 1939; abstracted, Am. J. Ophth. **23**:494, 1940.

196. Laqueur, L.: Ein Fall von beiderseitiger embolischer Iridocyclitis nach Influenza, Berl. klin. Wchnschr. **27**:816, 1890.

197. Duke-Elder,[1] p. 1984.

198. Burnet, F. M.; Jackson, A. V., and Robertson, E. G.: Intraocular Inoculation as a Standard Method for the Demonstration of Neutralizing Antibodies, Australian J. Exper. Biol. & M. Sc. **17**:253, 1939.

poliomyelitis virus as a standard method for the demonstration of neutralizing antibodies. The pathway from the eye to the brain was not demonstrated with certainty. The characteristics of the viruses mentioned will not be considered in this review because of the rarity or relative unimportance of the ocular complications.

OCULAR DISEASES OF SUSPECTED VIRUS CAUSATION

Acute Follicular Conjunctivitis of Béal.—This interesting and common type of acute follicular conjunctivitis has been known since Béal [199] described it in 1907 during an epidemic in Paris. The absence

Fig. 9.—Basophilic amorphous cytoplasmic inclusion bodies of Béal's acute follicular conjunctivitis, in conjunctival epithelial cells.

of bacteria and the obvious communicability of the disease have suggested a virus causation, but no etiologic studies have appeared. I have been unable to transmit the disease to any of the ordinary laboratory animals or to produce significant lesions on the chorioallantois of the developing chick embryo with secretion or epithelial scrapings. I have observed in considerable frequency round amorphous basophilic inclusions in the cytoplasm of epithelial cells (fig. 9).

199. Béal, R.: Sur une forme particulière de conjonctivite aiguë avec follicules, Ann. d'ocul. **87**:1, 1907. Morax, V.: Les conjonctivites folliculaires, Paris, Masson & Cie, 1933, p. 108. Thygeson, P.: Acute Follicular Conjunctivitis, Béal's Type, Arch. Ophth. **13**:853 (May) 1935.

Chronic Follicular Conjunctivitis.—This disease has been shown by Axenfeld [200] and Taboriski [201] to be transmissible from human being to human being, but no report of successful transmission to animals has appeared. The obvious communicability, as in orphanages and asylums, and the failure to demonstrate significant bacteria lend support to the hypothesis that the causal agent is a virus. I have been unable to demonstrate inclusions in epithelial scrapings or expressed follicular material.

Ocular Pemphigus.—There is still confusion as to terminology, interrelationship and relationship to pemphigus of those conjunctival diseases other than trachoma which lead to progressive cicatrization and shrinkage of the membrane. It would seem, however, that these conditions, usually referred to as ocular pemphigus but sometimes described as essential shrinkage of the conjunctiva, probably form an etiologic entity in which the causal agent may be a virus. German workers [202] have recently claimed the demonstration of virus-like elementary bodies in bulla fluid and conjunctival scrapings, and the production of transmissible and filtrable lesions in mice, a finding which has recently been confirmed by Grace and Suskind.[203] In a study of 4 cases of ocular pemphigus I was unable to demonstrate elementary bodies or to transmit the disease to baboons, rabbits or mice. Gallardo [204] recently obtained on three different occasions in a case of pemphigus-like cicatrizing conjunctivitis of fifteen years' duration a virus of large particle size closely resembling vaccinia virus. The disease could not be definitely identified with ocular pemphigus owing to the absence of other lesions of the skin or mucous membrane.

Dermatitis Herpetiformis (Duhring's disease).—Shrinkage of the conjunctiva occurs in this disease (Samuelson,[205] 1933), which has been ascribed to a virus by Urbach and Wolfram.[206] Bedson [207] produced

200. Axenfeld, T.: Bacteriology of the Eye, translated by A. McNab, London, Baillière, Tindall & Cox, 1908, p. 272.

201. Taboriski, J.: Ueber Trachom und Trachomähnliche Erkrankungen der Bindehaut, Arch. f. Ophth. **123**:145, 1930.

202. Wolfram, S.: Ueber den Nachweis granulärer Gebilde vom Typus der Virus Elementarkörperchen in den Efflorescenzen von Pemphiguskranken, Arch. f. Dermat. u. Syph. **178**:240, 1938.

203. Grace, A. W., and Suskind, F. H.: An Investigation of the Etiology of Pemphigus Vulgaris, J. Invest. Dermat. **2**:1, 1939.

204. Gallardo, E.: Personal communication to the author.

205. Samuelson, A.: Ueber Coactatio conjunctivae bei Dermatitis herpetiformis, Duhring, Acta ophth. **11**:501, 1935.

206. Urbach, E., and Wolfram, S.: Experimentelle und histologische Studien zur Frage des Virusgenese der Pemphiguserkrankungen, Acta dermat.-venereol. **15**:120, 1934.

207. Bedson, S. P., cited by Andrews, G. C.: Diseases of the Skin, Philadelphia, W. B. Saunders Company, 1939, p. 589.

vesicular eruptions on the plantar skin of guinea pigs with vesicle fluid, and Urbach and Reiss [208] produced paralysis and death in rabbits by injection of bulla fluid and blood from patients with the disease. Further work will be required to settle the problem of causation.

Uveitis.—It is a well known fact that herpes simplex virus and herpes zoster virus can cause inflammation of the uveal tract, and it has been demonstrated experimentally that the virus of lymphogranuloma venereum can also affect this tissue. It is possible, indeed, that the last-mentioned virus may be found to be an important cause of uveitis in human beings. The disease entity, generally known as Harada's disease,[209] consists of a bilateral uveitis of sudden onset, limited usually to the posterior segment and complicated with bilateral detachment of the retina, which eventually reattaches spontaneously with good visual results. Takahashi [210] in 1930 claimed successful transmissions to rabbits with fluid from the vitreous which was apparently free from microorganisms, and Togami [211] in 1931 confirmed his experiments. Rubino [212] traced the primary lesion of the disease to a benign lymphocytic meningitis and stated the belief that it is probably of virus origin. There are no records that "Harada's disease" is related to lymphocytic choriomeningitis, an established virus disease.

The possibility of a virus causation has been suggested for a number of other types of uveitis. Göscü [213] has described a case of recurrent aphthous stomatitis, probably due to a virus, accompanied by optic neuritis and iritis. No laboratory studies were made. Behcet [214] has reported a so-called triple symptom complex which he stated was a new disease entity characterized by aphthous ulcers of mouth and genitalia, retinitis and iridocyclitis and occasionally accompanied by cutaneous lesions resembling the lesions of erythema nodosum. The attacks were recurrent. He found inclusion bodies in 4 cases and considered a virus causation probable. Babel [215] in 1938 described a bilateral fibrinous

208. Urbach, E., and Reiss, F.: Tierexperimentelle Untersuchungen zur Frage der infektiostoxischen Genese des Pemphigus vulgaris und der Dermatitis herpetiformis Duhring, Arch. f. Dermat. u. Syph. **162**:713, 1930.

209. Harada, V.: Nippon Gankwa Gakukwai Zasshi **30**:356, 1926; cited by Duke-Elder,[1] 1941, vol. 3, p. 2366.

210. Takahashi, M.: Acta Soc. ophth. jap., 1930; cited by Magitot, A., and Dubois-Poulsen, A.: Le maladie de Harada, Ann. d'ocul. **177**:145, 1940.

211. Togami, K.: Acta Soc. ophth. jap. **35**:114, 1931; cited by Duke-Elder,[1] 1941, vol. 3, p. 2367.

212. Rubino, A.: Uveo-meningitisches Syndrom, Ophthalmologica **101**:955, 1940.

213. Göscü, N. I.: Regarding Some Cases of Recurring Aphthous Stomatitis Probably Due to an Infectious Virus, Accompanied by Optic Neuritis and Iritis, Türk oft. Gazetesi **2**:587, 1938; abstracted, Am. J. Ophth. **23**:955, 1940.

214. Behcet, H.: Some Observations on the Clinical Picture of the So-Called Triple Symptom Complex, Dermatologica **81**:73, 1940.

215. Babel, J.: Sur les symptômes oculaires dans la maladie des porchers, Ztschr. f. Augenh. **96**:159, 1938.

iritis as a part of the picture of a disease of swineherds (*maladie des porchers*) widespread in certain country districts in Switzerland, France and Italy. The aqueous from patients with the disease was sterile in culture mediums and failed to induce disease when injected into the anterior chambers of mice, rats and guinea pigs.

A virus causation for sympathetic ophthalmia was advanced as early as 1905 by zur Nedden,[216] who suggested that there might be a latent virus inhabiting the conjunctival sac which gained entrance to the eye after perforating injury. Even though no evidence to substantiate this hypothesis has been presented, it remains a distinct etiologic possibility in view of the failure to date to find any other cause for the condition.

Superficial Punctate Keratitis.—Superficial punctate keratitis in the form of minute epithelial erosions is a common finding in certain conjunctival diseases of bacterial origin, particularly staphylococcic conjunctivitis, and in a virus disease of the conjunctiva, trachoma, but there appears also to be a clinical entity of as yet uncertain causation characterized by punctate lesions located epithelially or subepithelially and associated with mild conjunctival inflammation. Grüter[217] sought to show that the disease was caused by herpes virus, as are some forms of disciform keratitis, but this virus can now be definitely eliminated as a cause. Wright[218] in 1930 found that the disease was transmissible to human beings and to black rabbits on corneal inoculation and claimed successful filtration. Such transmission has not as yet been confirmed, and more recently Wright[219] reported having observed intraepithelial bacilli in corneal scrapings from patients with the disease, apparently confirming the observation of Herbert[220] in 1901.

Epidemic Keratoconjunctivitis.—German writers[221] have since 1938 described a severe epidemic keratoconjunctivitis of uncertain causation. Its identity with or relationship to the various diseases known as superficial punctate keratitis (Fuchs, Wright), keratitis nummularis (von Stellwag, Dimmer) and acute follicular conjunctivitis (Béal) is still

216. zur Nedden, M.: Bakteriologische Blutuntersuchungen bei sympathischer Ophthalmie und anderen Formen von Iridochoroiditis, Arch. f. Ophth. **62**:193, 1905; cited by Duke-Elder,[1] 1941, vol. 3, p. 2332.

217. Grüter, W.: Bericht über die Zusammenkunft der deutschen ophthalmologischen Gesellschaft in Heidelberg, München. med. Wchnschr. **62**:162, 1920; **64**:220, 1924.

218. Wright, R. E.: Superficial Punctate Keratitis, Brit. J. Ophth. **14**:257 and 595, 1930.

219. Wright, R. E.: Discussion on the Rarer Forms of Keratitis, Tr. Ophth. Soc. U. Kingdom **57**:58, 1937.

220. Herbert, H.: Superficial Punctate Keratitis Associated with an Encapsulated Bacillus, Ophth. Rev. **20**:339, 1901; The Micro-Organism of Indian Superficial Punctate Keratitis, Brit. J. Ophth. **15**:663, 1931.

221. zur Nedden, M.: Beobachtungen an 500 Fällen von Kerato-Conjunctivitis epidemica, Klin. Monatsbl. f. Augenh. **105**:424, 1940.

obscure, but in my opinion it is probably identical with the epidemic superficial punctate keratitis described by Wright and others in India and the Far East. Epidemics of a similar and probably identical type of keratoconjunctivitis have recently occurred in Hawaii,[222] on the Pacific Coast and, still more recently, in New York. The infection in the Pacific Coast cases, as described by Hogan and Crawford,[223] started as unilateral follicular conjunctivitis with edematous lids, a swollen caruncle and semilunar fold and a scanty watery discharge. The second eye might become involved after a week. The corneas in from seven to twenty-one days showed definite epithelial infiltrates, which sometimes eroded and stained. In a few cases transient pseudomembranes appeared. In 90 per cent of the cases the preauricular glands were swollen and tender. Smears showed a lymphocytic exudate and a few diphtheroid bacilli, and cultures revealed no significant bacteria. The scanty mononuclear cell exudate suggested Béal's conjunctivitis, but its longer duration and the presence of corneal lesions differentiated the new condition from Béal's. It seems probable that it is a virus disease, and the work of Sanders [224] and Sanders and Alexander [224a] if confirmed would appear to establish it as such. Sanders isolated two strains of virus from patients with epidemic keratoconjunctivitis and was able to maintain them by mouse brain passage and by tissue culture on embryonic mouse brain in serum ultrafiltrate. The virus proved pathogenic for unweaned white Swiss mice when administered by the intranasal, intraperitoneal and intracerebral routes and for rabbits only when given by the intracerebral route. The pathologic changes in mice were limited to the central nervous system. The virus passed without difficulty through Seitz EK filters, through all grades of Berkefeld filters and through graded collodion membranes above 75 millimicrons average pore diameter. It passed with difficulty through membranes from 50 to 75 millimicrons average pore diameter but was consistently retained by smaller ones. The mouse virus was neutralized by serum from the 2 patients from which it had been isolated, as well as by serum from patients convalescent from epidemic keratoconjunctivitis in California and New York. A mild but characteristic picture of the disease occurred in a human volunteer inoculated with virus maintained by mouse brain passage.

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222. Holmes, W. J.: Epidemic Infectious Conjunctivitis, Hawaii M. J. **1**:11, 1941.

223. Hogan, M. J., and Crawford, G. W.: Epidemic Kerato-Conjunctivitis, Am. J. Ophth. **25**:1059 (Sept.) 1942.

224. Sanders, M.: Epidemic Keratoconjunctivitis, Arch. Ophth. **28**:581 (Oct.) 1942.

224a. Sanders, M., and Alexander, R. C.: Epidemic Keratoconjunctivitis, J. Exper. Med. **77**:71 (Jan.) 1943.

In a later report Sanders, Gulliver, Forchheimer and Alexander [224b] reported a study on 80 patients with the disease in which two additional strains of the virus were obtained. They called attention to the possible systemic nature of the disease, suggested by the fact that 49 of the 80 patients complained of headache (in 9 it was severe) and 26 of malaise. Of distinct interest was the finding that 70 of the 80 patients had been treated for ocular trauma or inflammation prior to the onset of symptoms, a fact suggesting office transmission. In view of the high communicability of the disease, these investigators recommended strict isolation of the patient and meticulous care to prevent spread from patient to patient by droppers, solutions, etc.

Severe Keratoconjunctivitis of Unknown Causation.—From time to time cases of severe keratoconjunctivitis of nonspecific character are noted in which bacteria cannot be demonstrated. The possibility that the disease in at least certain of these cases might be of virus origin led me to subject 5 of them to microscopic study for inclusions, to animal transfer experiments and to study by means of the chorioallantois of the developing chick embryo. All results were negative.

Chronic Catarrhal Conjunctivitis.—In view of the fact that significant bacteria are absent in many cases of chronic catarrhal conjunctivitis, I studied a number of such cases in an attempt to isolate a virus. Epithelial scrapings failed to show inclusion bodies or to induce lesions in animals or on the chorioallantois of the developing chick embryo.

Erythema Multiforme.—The association of a severe conjunctivitis, either purulent or pseudomembranous, with the oral and cutaneous lesions of erythema multiforme has been reported by numerous workers, but etiologic studies have so far failed to yield significant findings. In a recent investigation Edgar and Syverton [225] failed to demonstrate inclusion bodies or to produce lesions in experimental animals. I have observed 3 typical cases but was able to make etiologic studies in only 1. In this case, that of a boy of 9 years, there was a severe purulent ophthalmia together with a fulminating stomatitis and bullous dermatitis. Pus from the eyes failed to show significant bacteria or to infect the chorioallantois of rabbits and mice, but bulla fluid stained with Giemsa stain and Victoria blue revealed large numbers of small coccoid bodies having the appearance of virus elementary bodies. Bulla fluid failed to induce lesions in rabbits on subconjunctival and intraocular injection or in mice on intraperitoneal and intracerebral inoculation but did produce bacteria-free lesions of the chorioallantois and the death of the

224b. Sanders, M.; Gulliver, F. D.; Forchheimer, L. L., and Alexander, R.: Epidemic Keratoconjunctivitis, J. A. M. A. **121**:250 (Jan. 23) 1943.

225. Edgar, K. J., and Syverton, J. T.: Erythema Exudativum Multiforme with Ophthalmia and Stomatitis, J. Pediat. **12**:151, 1938.

embryo; similar coccoid bodies, though less numerous, could be demonstrated in scrapings from the membrane. The infection was carried through a second transfer to the chorioallantois but failed to take on a third. These findings suggest that a virus of large particle size may be the cause of the disease, and future cases should be studied with this possibility in mind.

ANIMAL VIRUS DISEASES WITH OCULAR MANIFESTATIONS

Periodic Ophthalmia of Horses.—This severe recurrent iridocyclitis of horses has been ascribed to a virus by Bossi [226] and by Woods and Chesney.[227] The latter authors passed a filtrable agent isolated from a diseased horse through 6 rabbits and then back to the horse, producing a typical disease with recurrences. The virus causation, however, cannot yet be considered as proved. Burky and co-workers [228] recently suggested that the condition may be a brucellosis, but this has been denied by Jones,[229] who failed to find Brucella organisms in 27 horses with the disease and by Stubbs and Love.[230]

Infectious Myxomatosis of Rabbits.—This virus disease of South American rabbits is characterized by tumor-like lesions of the skin and mucous membrane, particularly severe on the eyelids and conjunctiva. Filtrability of the virus has been shown by Moses,[231] Hobbs [232] and Findlay.[233] Its particle size has not yet been measured by differential filtration, but is evidently large, since the particles can be stained and can then be seen in the form of elementary bodies. According to

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226. Bossi, cited by Clark, H. C.: A Preliminary Report on Moon Blindness (Periodic Ophthalmia), in News Letter from the Horse and Mule Association of America, Chicago, Aug. 20, 1937.

227. Woods, A. C., and Chesney, A. M.: The Transmission of Periodic Ophthalmia of Horses by Means of a Filterable Agent, J. Exper. Med. **52**:637, 1930.

228. Burky, E. L.; Thompson, R. R., and Zepp, H. M.: The Rôle of Brucella in Human and Animal Ocular Disease with Special Reference to Periodic Ophthalmia in Horses, Am. J. Ophth. **22**:1210, 1939.

229. Jones, T. C.: The Relation of Brucellosis to Periodic Ophthalmia in Equidae, Am. J. Vet. Research **1**:54, 1940.

230. Stubbs, E. L., and Love, W. G.: Studies on the Relationship of Brucellosis to Periodic Ophthalmia, J. Am. Vet. M. A. **99**:476, 1941; Periodic Ophthalmia and Studies on the Possible Relationship to Brucellosis, ibid. **99**:142, 1941.

231. Moses, A.: O virus do mixoma dos Collhos, Mem. Inst. Oswaldo Cruz **3**:46, 1911.

232. Hobbs, J. R.: Studies on Nature of Infectious Myxoma Virus of Rabbits, Am. J. Hyg. **8**:800, 1928.

233. Findlay, G. M.: Notes on Infectious Myxomatosis of Rabbits, Brit. J. Exper. Path. **10**:214, 1929.

van Rooyen [234] the myxoma elementary bodies are slightly larger than the vaccinia bodies and measure about 0.3 micron in preparations made with Paschen's stain. When photographed at magnifications of 19,000 and 22,000 with the electron microscope, the elementary bodies appear to be oval in shape (von Borries and co-workers [235]). The inclusion bodies are acidophilic, amorphous and cytoplasmic.[236] The rabbit is the only known susceptible host.

Canine Distemper.—Conjunctivitis and keratitis occur frequently in dogs and ferrets suffering from distemper. The keratitis may be either ulcerative or interstitial and is occasionally accompanied by an iridocyclitis. The ulcers may sometimes perforate, with subsequent panophthalmitis and loss of the globe. The virus was first filtered by Carré [237] and later was studied completely by Laidlaw and Dunkin.[238] It is resistant to freezing and to drying and can be preserved in glycerin for several months. Cytoplasmic inclusion bodies 1 to 9 microns in size, resembling Negri bodies, have been found in epithelial cells of the respiratory tract and of the conjunctiva. According to Plummer [239] the virus will grow on the chorioallantois of the developing egg. An effective vaccine against the disease has been prepared.

Rickettsia-Like Organisms in Conjunctivitis in Animals.—In 1931 Coles [240] described the occurrence of a Rickettsia-like organism in an infectious keratoconjunctivitis of sheep in South Africa. It appeared to be the cause of the disease, and he named it Rickettsia conjunctivae. The same organism has been found in sheep in Algeria by Donatien

234. van Rooyen, C. E.: Elementary (Paschen) Bodies in Infectious Myxomatosis of the Rabbit (Virus Myxomatosum Sanarelli), Zentralbl. f. Bakt. **139**: 130, 1937.

235. von Borries, B.; Ruska, E., and Ruska, H.: Bakterien und Virus in übermikroskopischer Aufnahme, Klin. Wchnschr. **17**:921, 1938.

236. Rivers, T. M.: Infectious Myxomatosis of Rabbits, J. Exper. Med. **51**: 965, 1930.

237. Carré, H.: Experimental Researches on Neurotropic Dermatosis of Dogs: Canine Distemper, North Am. Vet. **8**:21, 1927.

238. Dunkin, G. W., and Laidlaw, P. P.: Studies in Dog Distemper: I. Dog-Distemper in the Ferret, J. Comp. Path. & Therap. **39**:201, 1926; II. Experimental Distemper in the Dog, ibid. **39**:213, 1926. Laidlaw, P. P., and Dunkin, G. W.: III. The Nature of the Virus, ibid. **39**:222, 1926.

239. Plummer, P. J. G.: Preliminary Studies of Distemper Virus on the Chorioallantoic Membrane of the Developing Egg, Canad. J. Comp. Med. **3**:96, 1939.

240. Coles, J. D. W. A.: A Rickettsia-Like Organism in the Conjunctiva of Sheep, Seventeenth Report of the Director of Veterinary Services, Union of South Africa, 1931, sec. 2, p. 175.

and Lestoquard [241] and in the United States by Johnson.[242] In 1933 Coles described a similar Rickettsia-like organism (reported in 1936 [243]) in the conjunctival epithelium of cattle and in 1935 [244] an organism in the conjunctival epithelium of goats suffering from conjunctivitis and keratitis. In the same year, while working in the United States,[245] he rediscovered the intracellular bodies originally described in 1910 by Uhlenhuth and Boing [246] as observed in conjunctival scrapings from pigs with conjunctivitis. This finding is of particular interest, since the German investigators confused these bodies with trachoma inclusions. In view of the close relationship between the Rickettsiae and viruses and the fact that certain of the ocular viruses, e. g. those of trachoma and inclusion blennorrhea, have one or more properties linking them with this group, it seemed pertinent to consider the following Rickettsiae in this survey:

Rickettsia Conjunctivae: This organism is found in a disease of sheep, generally known as infectious or specific ophthalmia, which appears as an acute purulent conjunctivitis and leads frequently to severe keratitis with corneal ulceration and rarely to panophthalmitis and phthisis bulbi. In the majority of cases, however, the eyes return to an apparently normal condition. The disease is most prevalent in spring and summer, and breed, age, sex and locality make no difference. In some years as many as 25 per cent of the sheep in South Africa become affected.

The disease can be transferred to normal sheep, the incubation period being from two to four days. Filtrations through "siliceous or plaster of paris filters" have been unsuccessful (Coles), and aerobic and anaerobic cultures have failed to show a significant bacterium. The virulent secretion becomes inactive in from forty-eight to seventy-two hours when kept at refrigerator temperature.

The Rickettsia-like organism believed by Coles and others to be the specific agent of the disease can be readily demonstrated in epithelial

241. Donatien, A., and Lestoquard, F.: La conjonctivite rickettsienne des ruminants, Rev. vet. et J. med. vet. et zootich. **91**:361, 1939; cited, Biol. Abstr. **14**:481, 1940.

242. Johnson, L. V.: A Pannus-Forming Infection of Sheep Eyes, Proc. Soc. Exper. Biol. & Med. **38**:42, 1938.

243. Coles, J. D. W. A.: A Rickettsia-Like Organism of the Conjunctival Epithelium of Cattle, J. South African Vet. M. A. **7**:4, 1936.

244. Coles, J. D. W. A.: A Rickettsia-Like Organism and an Unknown Intracellular Organism of the Conjunctival Epithelium of Goats, Onderstepoort J. Vet. Sc. **4**:389, 1935.

245. Coles, J. D. W. A.: A Rickettsia-Like Organism of the Conjunctival Epithelium of Pigs, Arch. Ophth. **25**:101 (Jan.) 1941.

246. Uhlenhuth, P., and Boing, W.: Chlamydozoenbefunde bei Schweinpest, Berl. klin. Wchnschr. **67**:1514, 1910.

scrapings from the conjunctiva stained by the Giemsa method; it is found inside the epithelial cells or extracellularly and occasionally in small numbers in neutrophils, probably as a result of phagocytosis. The organisms are small, averaging about 0.8 to 1 micron in length by 0.5 to 0.8 micron in width and are markedly pleomorphic, some forms showing polar staining suggestive of the initial body form of trachoma virus. They appear typically in a compact mass, either extracellular or intracellular and varying in size from an aggregation of as few as three or four organisms to one of as many as five hundred. They stain from a purplish red to blue with Giemsa stain, are gram-negative and not acid fast and stain with most of the bacteriologic dyes, such as fuchsin and methylene blue, although not as intensely as ordinary bacteria. The conjunctival secretion always shows a predominance of neutrophils at onset and during the period of acute symptoms.

In spite of the fact that as yet no arthropod vector, which is one of the requirements of typical Rickettsiae, has been found for this organism, Coles stated the belief that it is a new species of Rickettsia.

Rickettsia Conjunctivae Bovis: This Rickettsia-like organism, first described by Coles [243] in 1933 as occurring in ophthalmia of the ox, is found in the cytoplasm of conjunctival epithelial cells or occasionally free in the secretion. It exhibits a pronounced pleomorphism, the following forms occurring: (1) round forms, from 0.3 to 0.6 micron in diameter; (2) bipolar forms, averaging 1.0 to 1.5 microns in length and 0.5 micron in width, in which chromatoid material is aggregated at the ends and is thin along the sides; (3) bacillary forms, approximately the size of the bipolar forms, some showing a dense speck of deeply staining material in the center; (4) triangular forms, and (5) dumbbell forms, from 1.5 to 2.0 microns in length, indicating probable multiplication by binary fission. The cytoplasm of infected epithelial cells is usually packed loosely with the parasites, but sometimes there is dense packing of a portion of a cell suggestive of the inclusions of trachoma and inclusion blennorrhea.

The organism stains well with Giemsa stain, the smaller forms staining reddish blue and the larger bipolar forms a pure blue, much as the smaller elementary and larger initial bodies of trachoma stain. The organism is gram-negative and not acid fast.

There is almost always an associated neutrophilic response to the organism. The affected epithelial cells are not obviously swollen but do appear to degenerate and rupture. The organism does not invade the nucleus. It can be transmitted directly from eye to eye in infected secretion, with an incubation period of three days, but no clinical symptoms develop. Coles stated that although all attempts to transmit the

disease directly have failed, and it is therefore impossible to say that the organism is the cause of bovine ophthalmia, there is clearly a close relationship between the two, since the organism can always be found during the early phase of the disease if diligent search is made for it.

Rickettsia in Conjunctivitis of Hogs: An organism which Uhlenhuth and Boing [246] originally reported finding in the conjunctival epithelium of hogs with hog cholera occurs in an epidemic conjunctivitis in hogs in the form of inclusion-like masses. Morris [247] and I have failed to find these bodies in the conjunctiva in typical cases of hog cholera, however, and believe that the conjunctivitis probably bears no relation to hog cholera and that the German investigators were working with a mixed infection. The organism has the same morphologic and staining properties as Rickettsia conjunctivae bovis.

Rickettsia in Conjunctivitis of Goats: In morphology this organism closely resembles Rickettsia conjunctivae bovis, the forms varying from small round forms approximately 0.5 micron in diameter to bipolar forms 1.0 to 2.0 micron in length by 0.4 to 0.6 micron in width, with chromatoid material prominent at the ends but thin along the sides. The center is clear. It is not uncommon to find the whole conjunctival epithelial cell packed with the organism, and as many as 80 per cent of the cells may be affected. The organism stains well with Giemsa stain, the small round forms staining a bluish red and the large bipolar forms a reddish blue or pure blue. It is gram-negative and not acid fast and stains with the ordinary bacterial dyes but not so intensively as ordinary bacteria. The affected cells are not appreciably swollen but do show degeneration. The close association with the specific ophthalmia of the goat suggests that it is the cause, but definite proof has not as yet been offered.

Coccobacilliform Bodies in Infectious Catarrh of Mice: In 1937 Nelson [248] described a nasal catarrh in Swiss mice in which minute gram-negative organisms, which he referred to as coccobacilliform bodies, were demonstrated to be of etiologic importance. Many animals with the disease showed an associated conjunctivitis in which the same organisms could readily be demonstrated in conjunctival fluid.

In the conjunctival exudate of this disease the coccobacilliform bodies are usually numerous within epithelial cells. They may be so numerous that the cytoplasm of the cells under low power magnification looks roughly granular. They also occur in considerable numbers outside the cells and frequently within polymorphonuclear leukocytes. They are

247. Morris, M. C.: Role of Hog Cholera Virus in Production of Inclusions in the Conjunctival Epithelium, Proc. Soc. Exper. Biol. & Med. **32**:1281, 1935.

248. Nelson, J. B.: Infectious Catarrh of Mice, J. Exper. Med. **65**:833, 1937.

gram-negative and predominantly spherical, but elongated rod-shaped forms are occasionally noted. There are a few ring forms with narrow, stained rings and unstained centers. The discrete cells are often surrounded by a small clear halo. Nelson cultivated the bodies readily in tissue culture composed of minced chick embryo tissue in Tyrode solution, but attempts to obtain cultivation on ordinary bacteriologic mediums have failed. The bodies have passed through collodion membranes of a pore size which held back ordinary bacteria present in the exudate. They appeared to average between 0.3 and 0.4 micron in size. Tissue cultures which contained only the coccobacilliform bodies remained infective through as many as twelve transfers.

	Variola	Vaccinia	Herpes Simplex	Herpes Zoster	Varicella	Molluscum Contagiosum	Common Wart	Measles	Lympho Granuloma Venereum	Trachoma	Inclusion Conjunctivitis	Mumps
Inclusion Bodies	Cytoplasmic		Intranuclear			Cyto Plasmic *	Intra-nuclear	Giant Cells	Cytoplasmic			
Free Elementary Bodies	Present	Present	Present	Present?	Present?	Free Elementary Bodies			Free Elementary and Initial Bodies			
Animal Inoculation		Rabbit (Cornea)	Rabbit (Cornea)					Monkey's	Mouse (Brain)	Baboon (Conjunctiva)		Monkeys (Unsuccessful) (Parotid)
Egg Membrane Inoculation	Chorioallantois Lesions							Chorio-allantois Lesions	Yolk Sac			
Skin Reaction									Positive (Frei Test)			
Complement Fixation	Positive	Positive							Positive			
Tissue Culture	Positive	Positive	Positive	Questionable					Positive			
Biopsy			Intranuclear Inclusions			Typical Microscopic Picture				Characteristic Lymphofollicular Expression		

* Easily recognized in Giemsa stained smears or in unstained suspensions (examined by dark field) of expressed material

Fig. 10.—Laboratory findings in the ocular diseases known to be of virus origin.

LABORATORY DIAGNOSIS OF OCULAR DISEASES CAUSED BY VIRUSES

The clinical picture in such virus diseases as dendritic keratitis, trachoma, herpes zoster ophthalmicus and molluscum contagiosum is usually sufficiently characteristic to make diagnosis possible without laboratory aid. Occasionally, however, a laboratory diagnosis may be needed for confirmation in doubtful cases, particularly when herpes corneae, trachoma and molluscum contagiosum are in question. In other ocular virus diseases, such as the keratoconjunctivitis of lymphogranuloma venereum, laboratory diagnosis is mandatory, while in vaccinia and inclusion conjunctivitis laboratory confirmation is desirable. Figure 10 summarizes the laboratory procedures which are of diagnostic value.

635 West One Hundred and Sixty-Fifth Street, New York.

Correspondence

DESIGNATION OF VISUAL ACUITY

To the Editor:—Ophthalmologists are accustomed to designate their findings on visual acuity by referring to a standard distance (for instance, 20/50, 20/80). On the other hand, it seems that in all tests given by the military services, a standard size letter is used and the examinee has to approach this letter until he is able to read it. Therefore, the official designations of visual acuity for the military services read 12/20, 15/20, etc.

Examiners may have difficulty in comparing these two different kinds of designations. There is a simple way of conversion, by dividing the figure one wants to convert into 400. For instance: 20/25 of the ophthalmologists' designation equals 16/20 (400 divided by 25 equals 16), and 12/20 of the military services' designation equals 20/33 (400 divided by 12 equals 33).

Arthur Linksz, M.D., Hanover, N. H.

Dartmouth Medical School.

News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

American Board of Ophthalmology.—The American Board of Ophthalmology will hold examinations in New York city on June 4 and 5 and in Chicago October 8 and 9. Candidates will be required to appear for examination on two successive days. Formal application blanks may be procured from the secretary, Dr. John Green, 6830 Waterman Avenue, St. Louis.

Knapp Foundation Laboratories.—A new set of laboratories designed for the study of ocular functions, including physiologic optics, has been constructed and is now in operation at the Institute of Ophthalmology of the Presbyterian Hospital, Columbia-Presbyterian Medical Center, New York. These laboratories are being equipped and maintained by the Knapp Memorial Foundation, governed by Dr. Arnold Knapp, Dean Willard C. Rappleye and Dr. Phillips Thygeson. The laboratories are under the directorship of Dr. LeGrand Hardy. Current activities aside from teaching are largely concerned with the war and include studies of low illumination acuity testing and color discrimination tests.

Gullstrand Medal.—The Gullstrand medal has been awarded to Prof. Alfred Vogt, Zurich, Switzerland, by the Swedish Medical Society of Stockholm. This gold medal is awarded every ten years to the most outstanding contributor to ophthalmic research.

PERSONAL NEWS

Appointments to Knapp Foundation Laboratories.—Dr. Gertrude Rand, formerly associated with her husband, the late Prof. C. E. Ferree, at Bryn Mawr College and the Wilmer Ophthalmological Institute, has been appointed research associate at the Institute of Ophthalmology of the Presbyterian Hospital, Columbia-Presbyterian Medical Center, New York. She has been assigned to the Knapp Memorial Foundation laboratories for the study of optics and visual physiology. Dr. Rand has also been appointed Knapp Research Fellow at the institute.

Miss M. Catherine Rittler, technician in eikonometry and dark adaptation at the institute, has been appointed research assistant on the staff of the Knapp laboratories. Her new work includes study and evaluation of color discrimination tests.

Obituaries

S. HANFORD McKEE, M.D.
1875–1942

With the death of S. Hanford McKee, on Nov. 25, 1942, Canadian ophthalmology has lost a leader and American ophthalmology a kindly neighbor and friend.

Dr. McKee was born in 1875 in the province of New Brunswick and took his medical work at McGill University Faculty of Medicine, graduating in 1900. Soon becoming interested in ophthalmology, he went to Europe for training and spent there the years from August 1903 to June 1905. He worked chiefly in the clinics of Greef in Berlin and Axenfeld in Freiburg, Germany. From the latter he acquired an enthusiasm for bacteriology of the eye which remained with him through life and led to many original observations. He was one of the first ophthalmologists in this hemisphere to write on inclusion blennorrhea and to recognize the diagnostic value of the inclusions in trachoma. With Wolbach, the pathologist, he attempted to investigate the chemical nature of these inclusion bodies. He described some of the earliest cases of conjunctivitis due to the meningococcus and made many other reports of interesting bacteriologic observations.

Returning to Montreal, he began a service at the Montreal General Hospital which lasted until his death. He was director of the department of ophthalmology in the hospital from 1931 until 1941. He was an active and inspiring teacher at McGill University, serving first as demonstrator in bacteriology and ophthalmology. He became clinical professor in 1928 and chairman of the department in 1939.

He served in the Canadian Medical Corps throughout World War I. After serving with a hospital in France he was sent in command of a unit to the Island of Lemnos. Here he contracted amebic dysentery, which caused his return to England. After convalescence he was sent to a six hundred bed eye and ear hospital at Folkestone, England, which he later commanded. He returned to Canada in March 1919 with the rank of colonel, having received the C. M. G. and having been mentioned in dispatches twice.

In addition to his busy practice and teaching duties, he served in the Department of Pensions and National Health, and, although he had intended to retire from this in 1941, he could not resist the urgent duties which were assumed by that department at the beginning of the present war. Hence, in spite of a threatening hypertension, he continued this work, examining more than a hundred recruits a day, and it was undoubtedly this additional work which hastened his death.

He never lost his enthusiasm for teaching, writing and keeping up with his scientific societies. He was a regular attendant and participant in the meetings of the American Ophthalmological Society and the American Academy of Ophthalmology and Otolaryngology, being in great demand on the program of postgraduate courses of the latter and serving as its president in 1932. American ophthalmologists had come to feel that he was practically one of them, and, in spite of his native reserve, few men had more warm friends in these societies. His perfect honesty, practical judgment and sense of humor made him a delightful companion. In addition to exercising his interest in bacteriology, he was a sound clinician and an excellent ophthalmic surgeon. He was interested in medical ophthalmology, pathology and neurology, and his contributions on these subjects were full of practical wisdom and originality.

His place in Canadian ophthalmology will be difficult to fill, and his American colleagues will keenly miss his presence at the meetings to which he contributed so much.

He leaves a widow, Mrs. Shirley B. McKee.

SANFORD R. GIFFORD.

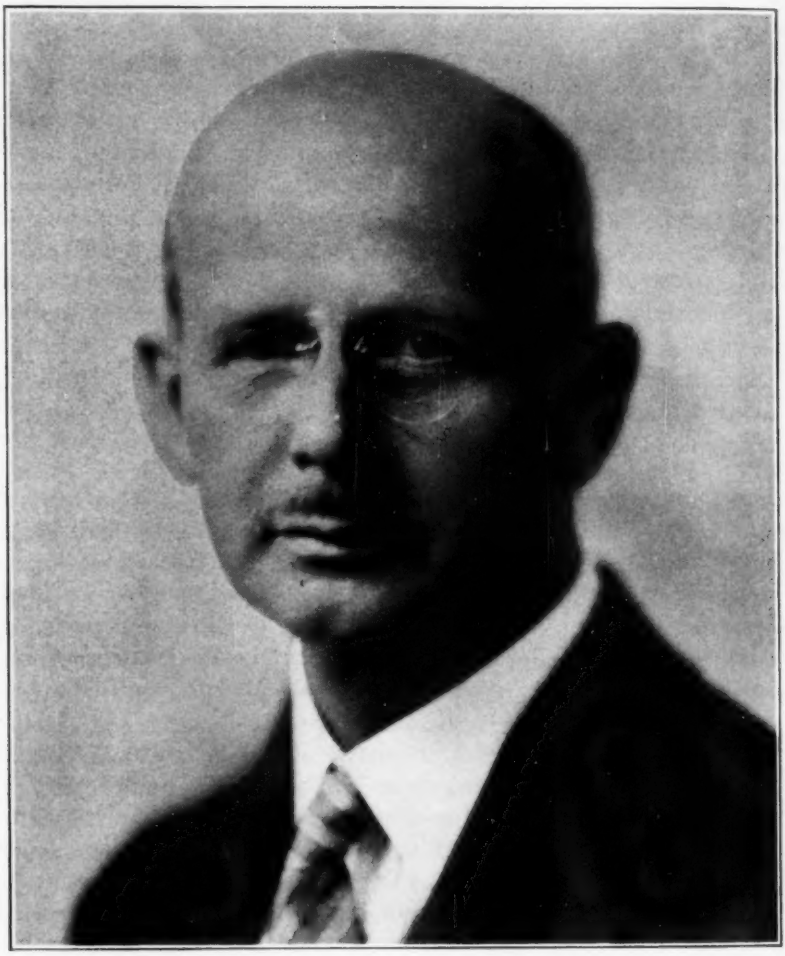
AN APPRECIATION

On Nov. 25, 1942 came to an end the long and useful career of one of the most distinguished ophthalmic surgeons of the day, Dr. S. Hanford McKee, M.D., C.M., F.R.C.S., of Canada, who was born in Fredericton, New Brunswick, in 1875. He was educated at the Model School in New Brunswick, where he won the Governor General's Gold Medal on graduation. On graduation from the University of New Brunswick he was awarded the Douglas Gold Medal; then followed his entry into McGill University, at Montreal.

After completion of his medical course at McGill University Faculty of Medicine, he was house surgeon to Dr. Frank Buller and to Dr. Birkett at the Royal Victoria Hospital for two years. A year as extern to that hospital was followed by two years of study in Europe, mostly under Professor Axenfeld in Freiburg, Germany. On his return to Montreal in 1905, Dr. McKee was appointed assistant oculist and aurist to the Montreal General Hospital and oculist to the Montreal Maternity Hospital. Later he became oculist to the Alexandra Hospital, Montreal Children's Hospital, Children's Memorial Hospital and Shriners' Hospital for Crippled Children and consultant to the Royal Victoria Hospital. His chief interest was always the Montreal General Hospital, where he finally became director of the department of ophthalmology and chairman of the medical board. He had great natural ability as a teacher, and McGill availed herself of his talents throughout his professional career, making him professor of ophthalmology in 1940.

He served as secretary of the Montreal Medico-Chirurgical Society from 1908 to 1924 and as president in 1925.

McKee's contributions to the literature of ophthalmology have been many and have covered various parts of the field; some of his papers have been in the nature of clinical reports, while the more important



S. HANFORD McKEE, M.D.
1875-1942

have been in the realm of original research, where he was particularly at home. One offering of McKee's which I believe to have been of unique value was the idea of bringing the laboratory into the daily routine of work in the clinic and consulting room. Convinced that the diagnosis of many of the so-called external ocular diseases could be simplified and confirmed by the use of simple laboratory procedures, he

was bold enough to make his own cultures, stain his own slides and examine them himself. This was the adopted routine at Freiburg in Axenfeld's day, and one could not but be impressed by the feasibility of the idea. Naturally some additional work is entailed, but that is of no importance when results are considered.

Genius has been defined as "an infinite capacity for taking pains," which aptly expresses the character of all of McKee's work. None of it was ever hurried or slipshod; all was done with infinite care and attention to details. In fact, McKee had a genius for work, which is suggested by the following incident: Asked by a friend to indicate what, if anything, had contributed to his success, McKee, after some hesitation, replied in these words: "When I came up to the University [McGill] I soon discovered that I had no better brain than the average, but then I found this, that I could do a day's work alongside of any of the men I was thrown with. Perhaps I capitalized on this ability; if so, it may be that what success I have had could be thus explained." Could it be that this is another way of saying that "genius is made up of one part inspiration and nine parts perspiration?" Along with the keenness for work was the determination on his part to be honest with himself and with the world—this was with McKee an article of his faith.

Medical politics for him did not exist, and politics in general, only so far as they affected his beloved Canada and the motherland. A more devoutly patriotic citizen it would be hard to find. His patriotism and his religion were not frequently discussed; they were things lived, but not talked about.

In 1914 he reported for duty with his unit within twenty-four hours of the declaration of war and was sent overseas almost immediately. He served at the front in Flanders, with the ill fated expedition to the Near East and in England. After four and one-half years of service he was able to doff his uniform and take up his practice again.

In the present war he immediately offered to join up but was ineligible on account of age. He continued, however, to carry on his work in the Montreal General Hospital, including the outpatient department, in addition to examining the troops, until the strain became too great, and he succumbed.

The ophthalmologic world will revere his memory for the lasting value of his writings, while those who were privileged to enjoy his personal friendship will mourn his loss and remember him always as the beloved physician, honored teacher, patriot and loyal friend—one who throughout his life put the achievement of a worthy goal above personal gain—and will say, with Pope, "An honest man's the noblest work of God."

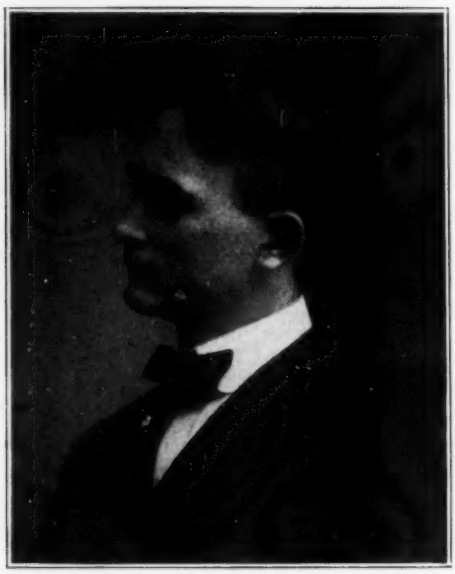
I think we shall not soon see his like again.

W. W. BLAIR.

CLARENCE ERROL FERREE, PH.D., D.Sc.

1877–1942

Dr. Clarence Errol Ferree, one time professor of psychology and director of the psychologic laboratories at Bryn Mawr College and professor of physiologic optics and director of the physiologic optics research laboratory at the Wilmer Ophthalmological Institute, died July 26, 1942 at Baltimore.



Prof. C. E. Ferree at Bryn Mawr, 1909.

Professor Ferree was born in Sidney, Ohio, on March 11, 1877. He received both the baccalaureate and the masters degree from Ohio Wesleyan University and became Sage fellow in psychology at Cornell University in 1902. He was awarded a Doctor of Philosophy degree from this institution in 1909. In 1939 Ohio Wesleyan conferred on him the Doctor of Science degree. Almost at the beginning of his professional life he turned his attention to the sensory functions and the evaluation of methods for their accurate control, recording and measurement. Experimental psychology in the Titchenerian sense became physiologic optics. This work continued for exactly a third of a century.

It was Professor Ferree's great good fortune to discover, in Gertrude Rand, one of the first two graduate students who came to him after he left Cornell, a mind which met, stimulated and supplemented his own.

His great talent was to stimulate others, to enliven their thinking, enrich their imaginations and direct their activities; hers, to comprehend the nature and direction of his aggressive drives, to weave them into a coordinated pattern and to bring fresh materials and methods for their furtherance. A happy working partnership was formed, which continued until his death. They were married, Ferree and Rand, on Sept. 28, 1918. Together they published more than two hundred and fifty articles, dealing largely with problems of vision.

Outstanding among the contributions of this gifted pair is their work on perimetry and the measurement of peripheral vision, the development of accurate radiometers for measuring visibile radiations, the testing of light sense, the multiple exposure tachistoscope, the study of visual acuity under low levels of illumination, industrial and hygienic illumination, flicker photometry and the measurement of refractive errors from the macula to the periphery.

Professor Ferree was a member of the Engineers Reserve Corps in World War I. He belonged to Phi Gamma Delta, Sigma Xi and Phi Beta Kappa (honorary) and was a Mason. He was a fellow of the American Association for the Advancement of Science and a member of the American Psychological Association, the Illuminating Engineering Society, the Optical Society of America, the Franklin Institute and the American Association of University Professors. He is survived by his wife, Dr. Gertrude Rand. They had no children.

In awarding Professor Ferree the degree of Doctor of Science on June 12, 1939, Acting President Edward L. Rice of Ohio Wesleyan summarized:

> By your intensive theoretical study you have brought light into the borderland where physics, physiology and psychology meet; by the application of your studies in practical invention you have aided oculists and opticians to bring light to defective human eyesight.

LE GRAND H. HARDY.

LT. COMDR. FRANK K. MOSS, U.S.N.R.
1898–1943

Lieutenant Commander Frank K. Moss, U. S. N. R., died while in active service at home with the United States Navy.

Commander Moss was born at Denver July 24, 1898. He held the degrees of Bachelor of Science and Electrical Engineer from the University of Colorado. For the past twenty years he had been associated with the General Electric Company in the Nela Park Laboratory. He was best known to ophthalmologists through his numerous publications in the field of lighting.

Commander Moss was a member of the Optical Society of America, the Illuminating Engineering Society and the American Society for the Advancement of Science.

He is survived by a sister, Mrs. Mildred M. Stadlinger, of Burbank, Ohio.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Anatomy and Embryology

MICROANATOMY OF THE EYE WITH THE SLITLAMP MICROSCOPE: II. COMPARATIVE ANATOMY OF THE CILIARY BODY, ZONULA AND RELATED STRUCTURES IN MAMMALIA. M. U. TRONCOSO, Am. J. Ophth. **25:** 1 (Jan.) 1942.

The technic of examination is described and observations on different animals recorded. A previous communication had to do with the structures of the angle of the anterior chamber. W. S. REESE.

AQUEOUS VEINS. K. W. ASCHER, Am. J. Ophth. **25:** 31 (Jan.) 1942

Ascher observed biomicroscopically, in living human eyes, vessels in the limbal and paralimbal regions containing highly diluted blood or a clear, colorless fluid, which emptied into the conjunctival and subconjunctival venous meshwork. He suggests that these be called aqueous veins and defines them as intermediary pathways between the intraocular fluid and the conjunctival and subconjunctival veins. He enumerates the characterics leading to their recognition. W. S. REESE.

Conjunctiva

CONJUNCTIVOCHALASIS. W. L. HUGHES, Am. J. Ophth. **25:** 48 (Jan.) 1942.

Hughes calls attention to a condition, for which he has suggested the name conjunctivochalasis, in which the lower part of the bulbar conjunctiva is very thin and more movable than normal. The symptoms are pain, irritation and repeated subconjunctival hemorrhages. Treatment consists of excision of a crescentic strip of conjunctiva.

W. S. REESE.

OPHTHALMIA NEONATORUM: THE ETIOLOGY IN 62 CONSECUTIVE CASES. S. H. MCKEE, Am. J. Ophth. **25:** 52 (Jan.) 1942.

McKee found cytoplastic inclusion bodies in 42 of 62 cases of ophthalmia neonatorum. He concludes that inclusion blennorrhea forms a large part of the ophthalmia of the newborn. He has found sulfanilamide administered by mouth beneficial, as it is also in cases of gonococcic and of mixed infection. W. S. REESE.

SULFATHIAZOLE IN THE TREATMENT OF GONORRHEAL EYE DISEASE. C. R. MULLEN, Am. J. Ophth. **25:** 59 (Jan.) 1942.

Mullen found that sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) used locally and internally in 5 cases of gonorrheal disease of

the eye gave as satisfactory results as those obtained from sulfanilamide used similarly. He stresses the importance of frequent irrigations.

W. S. Reese.

Verruca as a Cause of Unilateral Conjunctivitis. C. A. Turtz, Am. J. Ophth. **25:** 452 (April) 1942.

Turtz reports 2 cases of unilateral conjunctivitis of long duration and resistant to all forms of local treatment until warts, almost hidden by thick lashes, were removed. He calls attention to the opinion that warts are produced by a filtrable virus and are autoinoculable and infectious.

W. S. Reese.

Inclusion Conjunctivitis. A. F. MacCallan, Brit. J. Ophth. **26:** 271 (June) 1942.

MacCallan describes the various types of inclusion conjunctivitis, states the differential diagnosis between these diseases and trachoma and gives the treatment by sulfonamide compounds.

W. Zentmayer.

Inclusion Body Conjunctivitis and Trachoma with Reference to the Cells Observed in Smears. S. Oishi, Klin. Monatsbl. f. Augenh. **105:** 263 (Sept.) 1940.

Oishi reports on his clinical experiences with inclusion body conjunctivitis and trachoma. He found Prowaczek's bodies and Linder's initial bodies in 87 of 850 cases of genuine trachoma, which had not been treated before, and of suspected trachoma, and in 11 of 17 cases of nongonorrheal blennorrhea neonatorum. Mononuclear leukocytes were found in every one of the smears containing Prowazek bodies, in about 77.7 per cent of the cases of inclusion conjunctivitis and in 64.4 per cent of the cases of inclusion blennorrhea, whereas they were found in only 20.5 per cent of the cases of typical trachoma and of other types of infectious conjunctivitis. This count remained unaltered for the chronic stage. Inclusion conjunctivitis is accompanied by acute and diffuse papillary swelling, numerous follicles and swelling of the preauricular gland. The author concludes that conjunctivitis in which Prowazek bodies are present is not trachoma but genuine inclusion body conjunctivitis.

K. L. Stoll.

Cornea and Sclera

Dendritic Keratitis. J. O. Wetzel, Am. J. Ophth. **25:** 409 (April) 1942.

Wetzel briefly reviews the history of, experimental work on and the treatment of dendritic keratitis. He considers the local application of iodine the preferred therapy.

W. S. Reese.

TRANSPLANTATION OF THE CORNEA OF THE CADAVER. H. ARRUGA, Ophthalmological Society Hispano-Americana, Madrid, October 1941.

The author adds some new data to his work, published two years ago, on the transplantation of the cornea from the cadaver. He emphasizes the difficulty of comprehending the causes that produce the opacification of the graft. It is known that the greater the transparency of the receiving cornea, the more favorable will be the results, but there are paradoxic results that are not in accord with what seems logical, for instance the good results with grafts from corneas conserved for several days compared with those with grafts treated with solution of formaldehyde and the favorable results obtained in cases of corneal degeneration. Good results are obtained when the cornea is vascularized when the vascular supply was reduced by the operation. The opacification of the graft which appears immediately on transplantation is benign, as it disappears as completely as in those cases in which it appears late and develops slowly.

The hyperemia of the globe is no obstacle to a good result. The author presented a patient whose eyes had been operated on twenty-two months and sixteen months before, respectively, with resulting vision of 5/10 and 1/10.

W. ZENTMAYER.

General Diseases

EFFECT OF UNDERNOURISHMENT ON THE EYES. L. ORTIN, Arch. Soc. oftal. hispano-am. **1:** 1, 1942.

This article is based on the observation of some 500 undernourished patients with ophthalmic disease at Madrid during the Spanish Civil War. In some the symptoms were purely subjective. Either there was slowly progressive or fulminating loss of vision, or words seemed abbreviated or distorted. Scotomas were present in 50 per cent; these were central in the majority, paracentral in less than 10 per cent and disseminated in a few. Depression of the field was unusual. Color perception was good. Dyschromatopsia with reversal of the usual order of color perception was noted.

Day blindness was rare, but night blindness was more frequent. The external conditions encountered were blepharitis, conjunctivitis and keratoconjunctivitis. Fundus changes were classed, in order of frequency, as hyperemic, edematous and mixed. The principal general symptoms were a considerable loss of weight, asthenia, frigidity of the extremities, painful paresthesias, loss of memory, scorbutic stomatitis, cutaneous manifestations, pellagroid, petechias and purpura.

W. ZENTMAYER.

Glaucoma

GONIOTOMY. S. T. CLARKE, Am. J. Ophth. **25:** 423 (April) 1942.

Clarke gives the following summary and conclusions:

"The goniotomy operation is discussed with the presentation of a possible rationale for its use. Types of cases suitable for its use and difficulties encountered in the surgical procedures are brought out.

Eight cases in which this operation was used are briefly presented. Results were successful in seven. Certainly there should be a limited place for this operation in the armamentarium of glaucoma surgeons."

W. S. REESE.

Injuries

SOME OCULAR INJURIES MET WITH ON THE WITWATERSRAND GOLD MINE. P. H. BOSHOFF, Proc. Transval Mine M. Officers' A. **22:** 103 (May) 1942.

Boshoff discusses the injuries met with under two headings: (1) injuries without retention of a foreign body, e. g. contusions, dislocations, concussions and ruptures, and (2) injuries with the retention of a foreign body, which may be penetrating or nonpenetrating.

He advises the use of atropine sulfate for "red" eyes, as by this method thousands of traumatized eyes will be saved to one aggravated into glaucoma. The "atropine glaucoma" bogey is grossly overdone in teaching institutions. Boshoff has found the following technic useful for obtaining a roentgenogram when a suspected foreign body within the eye is suspected. The broad side of a dental film is inserted between the eye and the inferior orbital margin. It is pushed in in this horizontal position, and the patient is instructed to look slightly downward while the central roentgen ray is directed on to the film so that it just escapes projecting the shadow of the superior orbital margin. Similarly, the corner of a dental film in the vertical position is pushed into the median angle of the eye while the patient looks directly forward. The central roentgen ray in this position just misses the lateral orbital margin. Both these procedures give a soft tissue picture of the eye up to the depth corresponding roughly to the center of the lens. W. ZENTMAYER.

Lens

WOUND RUPTURE AFTER CATARACT EXTRACTION. H. S. GRADLE and H. S. SUGAR, Am. J. Ophth. **25:** 426 (April) 1942.

Gradle and Sugar draw the following conclusions:

"We believe that rupture of the wound after operation for senile cataract is due to increased intraocular pressure brought about by forcible contracture of the orbicularis and/or the recti and oblique muscles. Compressibility of the eyeball within the orbit is approximately the same in all normal eyes, and hence is not to be regarded as a factor in wound rupture. In the series of cases studied, the degree of bulbar proptosis made little difference in the end results, although it is probable that in instances of definite exophthalmos it would be an important factor in causing wound rupture.

"Tenotomy of the orbicularis as a means of preventing orbicularis action during the postoperative danger period gave excellent results in a series of 40 private cases, whereas in 52 clinic patients the results were approximately the same as in a series of nontenotomized cases. A further study in a larger series of cases will be made." W. S. REESE.

ALTERATIONS IN THE CAPSULAR EPITHELIUM IN IMMATURE CATARACTS. C. A. CLAPP, Am. J. Ophth. **25:** 437 (April) 1942.

Clapp gives the following summary and conclusions:

"1. Seventy cases of immature cataract removed in their capsules were studied.

"2. Atrophy of the capsular epithelial cells was found in practically all the cases.

"3. Proliferative changes were found in a few.

"4. Migration of the nuclei of the capsular epithelium is often marked.

"5. Alterations in, and death of, the capsular epithelium would seem to be a cause rather than a result of the lens changes." W. S. REESE.

MULTILAMELLAR CATARACT WITH GLOBULES: REPORT OF A CASE. M. BÜCKLERS, Klin. Monatsbl. f. Augenh. **105:** 312 (Sept.) 1940.

Bücklers reports on a girl aged 6 whose family history showed no consanguinity, no rachitis and no tetany. The parents noticed that the pupils turned gray while the child had measles when 3 years old. Four layers could be noted in the lens, and diffusely reflecting spheroids were formed in the second and third layers. A number of round pearls were observed at the equator of the inner layer and smaller ones of a similar type on the anterior surface of the outer layer. Such pearls were observed by Axenfeld and Stock in cataracta zonularis. The larger pearls found at the equator occur rarely. They consist of calcium phosphate (Wessely). This rare type of concentric layers in lamellar cataract was observed in hereditary cataracta pulverulenta. The dotted opacities, however, were finer, dust shaped and more closely packed in Bücklers' case than in cataracta pulverulenta. The cortex was barely cloudy between the opaque shells. The described formation may have developed prior to or after birth. It is uncertain whether this cataract was of an endogenous or exogenous nature or was caused by determinative or chemiconutritive influences. K. L. STOLL.

Methods of Examination

PRACTICAL MULTIPLE VISUAL SCALE FOR FUNCTIONAL EXAMINATION OF EYE. R. ARGAÑARAZ, Arch. de oftal. de Buenos Aires **16:** 536 (Sept.) 1941.

A transparent single optotype, with multiple scales, is here described. It makes possible the usual subjective examination of literate patients; examination of illiterate subjects and young children; subjective determination of astigmatism and its axis; study of the muscle balance of the eye with the Prentice scale and Maddox rod, with diagnosis of orthophoria, exophoria and esophoria by means of the Maddox rod or the Thorington arrow, and determination of central chromatic perception for red, green, yellow and blue at a distance.

The simplicity and relatively small size of this model (0.6 by 0.8 meter) allows a practical and rapid functional examination in the dark chamber. C. E. FINLAY.

Neurology

TEMPORARY AMAUROSIS AND HEMIANOPSIA DUE TO EPILEPSY. A. KING and F. B. WALSH, Am. J. Ophth. **25:** 398 (April) 1942.

King and Walsh describe 2 cases, one of blindness and the other of homonymous hemianopsia following severe generalized convulsions. They believe that a majority of cases of blindness following epilepsy, and certainly those in which the pupillary reflexes remain intact or in which hemianopsia is present, are best explained on the basis of temporary exhaustion of the visual cortex due to epileptic discharge.

W. S. REESE.

TWO FORMS OF SCINTILLATING SCOTOMAS AND THEIR PROGNOSTIC VALUE: REPORT OF CASES. C. ADAM, Klin. Monatsbl. f. Augenh. **105:** 211 (Aug.) 1940.

Toward the end of a strenuous trip through Italy, Sicily and Libya in the fall of 1937, 3 of Adam's associates complained of scintillating scotomas. Adam quieted their uneasiness by stating that he had been troubled with scotomas for ten years. However, 2 of the 3 men, aged about 60, died of apoplexy during the following year. The author was aware of the existence of two forms of scotomas, the first hereditary, appearing in youth and decreasing with age, and the second the result of anatomic changes evident later in life. The second form may be subdivided into scotomas caused by diseases of the central nervous system, such as multiple sclerosis and brain tumor, and those brought on by senile changes in the blood vessels of the brain.

Adam sent a questionnaire to a number of experienced ophthalmologists and neurologists and received numerous answers, a résumé of which is given. The menopause, trauma to the brain and vascular changes due to nephritis were mentioned as causes of the first, or "juvenile," form. As etiologic factors for the second, or senile, form, appeared red hypertension, sclerosis of the blood vessels, coronary sclerosis, infarct and myodegeneration of the heart. Thiel found narrowing of the retinal vessels coupled with scintillating scotomas. Adam found these scotomas brought on by abuse of nicotine and alcohol, hunger after missing a meal, lack of rest for a number of nights, dietary irregularities, professional strain and intensive exposure to the sun or to cold. The prognosis is generally not unfavorable; patients are referred to who observed scotomas of the senile type for ten to twenty years.

K. L. STOLL.

Orbit, Eyeball and Accessory Sinuses

RHINOGENIC OPTIC NEURITIS AND OCULO-ORBITAL COMPLICATIONS OF SINUSITES. R. ARGAÑARAZ, Arch. de oftal. de Buenos Aires **16:** 541 (Oct.) 1941.

The intimate anatomic relations of the orbit with the neighboring nasal cavities are stressed, as well as the likelihood of infection from

these cavities not only of the cellular tissue of the orbit but of the membranes of the eyeball and its neurosensorial apparatus.

Argañaraz classifies the ophthalmic complications of sinus trouble into (1) an anterior frontal-ethmoid-maxillary group and (2) a posterior sphenoid-ethmoid group. It is well, however, to remember that only rarely is a single sinus affected, monosinusitis being the exception and polysinusitis the rule.

The first group comprises: (1) orbital cellulitis and abscess, (2) iritis and iridocyclitis and (3) oculomotor and sensory palsies. Orbital cellulitis and abscess are always of secondary origin and are due mostly to the streptococcus and less frequently to the pneumococcus or the staphylococcus. When the cause is a thrombosis of the cavernous sinus, the outcome is usually fatal, with rapid involvement of the optic nerve and its sheaths and destruction of vision.

A consideration of the second group constitutes the major part of the article. Their origin from ethmoid and sphenoid sinusitis is readily explained by the intimate relations of the optic nerve in its intracranial portion with the sphenoid sinus and posterior ethmoid cells.

The originating sinus trouble is mostly a part of general polysinusitis and may exist in a latent form. The visual symptoms are often the first to demand attention. A roentgen examination is required but at times gives negative results. The extension to the optic nerve and its sheath is generally direct, but occasionally it is through venous anastomosis. Reference is made to cases in which no inflammatory signs are apparent but in which the visual symptoms improve on opening of the sinus or on application of cocaine and epinephrine hydrochloride or of benzedrine. The functional disturbances in these cases are explained on the basis of changes in the sympathetic vascular innervation. Some varieties of retrobulbar neuritis are attributed to opticochiasmatic arachnoiditis. In the optic nerve the maculopapillary bundle of fibers is often affected.

Clinically, the onset of retrobulbar neuritis is most often acute and unilateral, with the production of a central scotoma of from 20 to 50 degrees. The disease generally lasts two to three weeks, disappearing gradually on improvement of the rhinitis. Subacute forms also occur with a scotoma of from 10 to 20 degrees. There is an accompanying increase in the size of the blindspot. As a rule there are no ophthalmoscopic signs at first. If the process is intense and of long duration, pallor and finally optic nerve atrophy are apt to occur.

The differential diagnosis is concerned with the retrobulbar neuritis of multiple sclerosis, with that of opticochiasmatic arachnoiditis and with the toxic form.

As to treatment, many cases terminate favorably with medical and local treatment, the latter consisting of applications of cocaine and epinephrine hydrochloride to the nose in the proximity of the opening of the sphenoid sinus. If any general catarrhal symptoms are present, they must be attended to. When these simple measures give no relief, surgical opening of the sphenoid sinus must be resorted to.

C. E. FINLAY.

Society Transactions

EDITED BY DR. W. L. BENEDICT

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC.

ALGERNON B. REESE, M.D., *Chairman*

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Thirteenth Scientific Meeting, Atlantic City, N. J., June 9, 1942

Quantitative Study of the Cells and Fibers in the Nucleus-Nerve Complexes of the Fourth and Sixth Cranial Nerves. ROBISON D. HARLEY, M.D., PH.D., Rochester, Minn. (Paper read by Dr. W. L. Benedict).

There is clinical and physiologic evidence that there must be connections between the different oculomotor nuclei because of the smooth interplay and reciprocal action that exists between the eye muscles, not to mention further nervous pathways connecting the nuclei of the midbrain to the nuclei of the hindbrain and even the spinal cord. The problem is the location of the cell stations of these oculomotor connections. In this study the numerical relationship between fibers and cells of the fourth and sixth cranial nerves and nuclei has been established. If there are fewer cells than motor fibers a part of the cells of origin must lie outside the circumscribed masses of gray matter which are the respective nuclei. More cells than fibers, on the other hand, would indicate that there must be nervous connections other than to the peripheral nerve, the fibers of which are supplied at least by some of the cells of these nuclei.

The nerve and nucleus specimens were collected from 32 normal human brains, but owing to multiple samples 113 fourth nerve sections, 77 sixth nerve sections, 53 fourth nerve nuclei and 49 sixth nerve nuclei were actually analyzed. Each nerve was studied to determine the number of myelinated nerve fibers and also the total number of fibers. The nuclei were sectioned serially at 10 microns, and every tenth section was analyzed for the total number of motor cells present.

It was found that the mean number of cells for the nucleus of the fourth nerve was 2,383 and the mean number of fibers 2,147. For the sixth nerve the mean number of cells of the nucleus was found to be 6,154 and the mean number of fibers 5,176. No significant difference was found between the right and the left side with respect either to the number of cells or to the number of fibers. The number of cells in the nucleus was found to exceed the number of fibers in the corresponding nerve in almost all instances. The cell-fiber ratios were also studied, and the mean values for the same four nucleus-nerve complexes were 1.11, 1.15, 1.21 and 1.19. The relationship of cells to fibers was also studied graphically with the aid of fitted regression lines.

The number of unmyelinated fibers, as determined by the difference between the total number of fibers and the number of myelinated fibers, was 150 for the fourth and 440 for the sixth nerve. The average length of the nucleus was 2.4 mm. for the fourth nerve and 3.3 mm. for the sixth nerve. The mean cross sectional areas for the corresponding nerves were, respectively, 0.22 and 0.59 sq. mm.

The fourth and sixth cranial nerves belong to the type of mixed nerve whose afferent fibers convey pain and the proprioceptive sense.

According to the work of Bjorkman and Wohlfart and Zotterman, one may estimate that at least 39 per cent of the fibers of the fourth nerve and 22 per cent of those of the sixth nerve are sensory. Making use of these figures, one finds about 85 per cent more cells than motor fibers for the fourth nucleus-nerve complex and, similarly, over 50 per cent more cells than motor fibers for the sixth complex.

Since there are clearly more cells in the so-called nuclei than motor fibers in the peripheral nerves, it is logical to assume that the motor nuclei of the fourth and sixth cranial nerves send fibers not only peripherally into these nerves but centrally to other regions, such as other cranial nuclei, probably via the median longitudinal fasciculus. Some of the association mechanism (association centers) may thus be within the confines of the so-called nuclei of the ocular nerves.

DISCUSSION

DR. H. J. SMITH, Chicago: I should like to ask Dr. Benedict if any proof was found for the theory that some of the cells in the nucleus of the fourth nerve, where one cannot find fibers connected with them, are for correlation with the nucleus of the opposite side. I have not been able to find any such evidence in the literature, but interconnection occurs in so many parts of the nucleus of the third nerve that I wonder whether there could be any decussation with the nucleus of the opposite side in the case of the fourth nerve. I do not know anything about the sixth nerve in that regard, but I suspect that there is no decussation.

DR. W. L. BENEDICT, Rochester, Minn.: I think that Dr. Harley did not assume terminal association. His work had to do with the actual count. On the other hand, the deviation, the individual variability between the right and the left side, was statistically insignificant, and there appeared to be nearly equal excess of cells over fibers on both the right and the left side; so it is quite possible that there was a direct relationship, although this is purely an assumption. How many of the fibers may go to the nucleus of the third nerve or of the sixth nerve, or whether they go to some other nucleus, there is no way of knowing, but it is presumed that there is a sufficient excess of cells over fibers for such an association to be possible.

In going over some of the specimens, Dr. Harley rather felt that probably some of those nuclei were idle and that they had no connection with any other source. At any rate, he was not able to trace, except in myelinated fibers, any other group of fibers to these cells. They simply exist there, but what connection they have, he was not able to determine.

DR. FREDERICK H. VERHOEFF, Boston: In other words, one cannot draw any conclusion from the study?

DR. W. L. BENEDICT, Rochester, Minn.: No.

DR. FREDERICK H. VERHOEFF, Boston: Dr. Harley spoke of proprioceptor fibers. The evidence is that there is no proprioceptor for the ocular muscles. The work done by Ludvigh and Irvine indicated clearly that the old idea that the eye is not dependent on a proprioceptive sense is true, and, therefore, one need not consider proprioceptor fibers in this connection at all.

DR. W. L. BENEDICT, Rochester, Minn.: It is assumed that those fibers that were not myelinated motor fibers were sensory, but Dr. Harley did not say whether they were proprioceptive or not.

Intrascleral Vascular Plexus and Its Relations to Outflow of Aqueous.

DR. MANUEL URIBE TRONCOSO, New York.

The anatomic arrangement of the vessels in the angle of the anterior chamber has a considerable influence on the movement and rate of the outflow of aqueous.

In previous articles I have shown that there is a great difference in the anatomic building of this region between lower mammals and primates. In rodents and in ungulates there is a cleft between the sclera and the outer side of the ciliary body which is filled with aqueous and communicates with the anterior chamber through the so-called Fontana spaces. To this cleft I have given the name "cilioscleral sinus." In rabbits it is made of large spaces, but in ungulates it is filled up with a peculiar spongy tissue. On both sides of the cleft there are numerous vessels. On the outer wall there is a rich vascular network in the thickness of the sclera called "intrascleral plexus." Some of its branches are very superficial, their endothelial wall coming in direct contact with the aqueous, through the network of the trabeculae. These veins have been compared to the Schlemm canal in man, but, as they have different anatomic characteristics, would properly be called trabecular veins. In these animals the whole cilioscleral sinus performs the physiologic function performed by the Schlemm canal in primates. On the ciliary body side of the cleft there are also vessels which come in contact with the aqueous.

In carnivores the sinus is entirely filled with numerous fine strands, which are tendons of the ciliary muscle. They are closely packed, and to facilitate absorption of aqueous the intrascleral vascular plexus is exceptionally rich. It is lodged in large cavities inside the sclera, the Hovius ring.

In primates the anatomic arrangement is different. The cilioscleral sinus has disappeared, owing to the enormous development of the ciliary muscle. A new organ has appeared, the Schlemm canal, which is lodged in a special groove in the sclera above the spur. The whole intrascleral plexus has moved forward. It is connected with the Schlemm canal by a few branches, called "collectors" (there are from twenty to thirty around the limbus), while the rest of the plexus has numerous richly interlacing branches. The Schlemm canal is really a small plexus in itself. Leber called it a venous sinus; Swindle, one of the many veins of the intrascleral plexus. These opinions are not tenable, however, since with the gonioscope the Schlemm canal appears filled with aqueous and only rarely is seen to contain blood. Friedenwald has found fine arteries connecting directly with the lumen of the canal.

From the physiologic standpoint the absorption of aqueous is different in lower mammals and in primates. In the former the endothelial

wall of the trabecular veins forms the blood-aqueous barrier. Absorption of aqueous takes place especially at the venous exits of the capillaries by a combination of hydrostatic and osmotic pressure.

In primates conditions are different; there is no blood-aqueous barrier. The Schlemm canal is normally filled with aqueous absorbed by a combination of hydrostatic and osmotic pressure. In the rest of the intrascleral plexus blood pressure is lower and aqueous passes directly into the blood through the collector channels. A slight amount of plasma leaks backward, normally into the canal; but if blood pressure is increased, red corpuscles may penetrate into it.

DISCUSSION

DR. K. W. ASCHER, Cincinnati: Detection of the fact that the aqueous-venous channels change continually with elimination of fluid out of the human eye is unexpected confirmation of the latest theory and of the most interesting anatomic and physiologic details described by Dr. Troncoso.

Corneal Permeability: Factors Affecting Penetration of Drugs Into Cornea. DR. KENNETH C. SWAN and NORMAN G. WHITE, M.S., Iowa, City.

Passage of drugs through the cornea into the globe is generally considered to be a process of diffusion. The rate is believed to be affected by variations in osmotic pressure, p_H and concentration of the test solution, as well as by the condition of the surface epithelium. Disturbances of the surface epithelium are known to increase corneal permeability to drugs. In addition, it has been assumed by some authors that the relative permeability of the cornea to various compounds is in inverse relation to the size and complexity of the individual molecules. However, other physical properties of compounds have received little consideration in studies of corneal permeability, although lipid solubility, surface activity, electrical charges and diffusion coefficients are known to affect the penetration of substances into the various plant and animal cells. The recent use by O'Brien and Swan of a surface tension–reducing vehicle, zephiran, to increase absorption of carbaminoylcholine (doryl) suggests that at least one of these factors is of importance in relation to the cornea. These authors suggested also that the relative impermeability of the cornea to choline derivatives might be explained by the difference in physical properties of these compounds as compared with the alkaloids.

To study these possible new factors and correlate them with older conceptions required investigation of the entire problem of corneal permeability. Factors affecting the rate of penetration into the cornea were studied as an initial phase. Other phases of corneal permeability will be considered in subsequent reports.

The relative rates of penetration into the cornea of a group of naphthalene derivatives of similar molecular structure were determined and correlated with the physical properties of the compounds and their solutions. These compounds were selected for study because it was possible to change their physical properties by varying the number and position of polar amine and sulfonic acid groups on the nonpolar naphthalene nucleus. Moreover, they were fluorescent, permitting biomicro-

scopic study of the penetration into the ocular tissues as well as quantitative chemical analyses. In addition, relative rates of penetration into the cornea of a group of local anesthetics were investigated. The anesthetics selected were similar to each other in molecular weight and structure but had varied physical properties in accordance with changes in relationship between the nonpolar and polar groups. Moreover, the physical properties of the free anesthetic bases differed considerably from those of the salts, permitting another type of correlation to be made between physical properties and rates of penetration.

The various test substances varied in rate of penetration into the cornea. Several of the relatively nonpolar compounds penetrated many times more rapidly than relatively polar compounds of the same chemical group. Superficial lesions of surface epithelium decreased the differences in penetration rates, which indicated that the epithelium acted as a membrane with differential permeability. This differential permeability appeared to be closely related to the physical properties of the test substances. Physical properties of the drug vehicles were found to be of importance also. Possible therapeutic applications of the results of these studies were discussed.

DISCUSSION

DR. JONAS FRIEDENWALD, Baltimore: I believe that Dr. Swan's work has brought the problem of the permeability of the cornea in line with that of the permeability of many other organs. I think that his statements have greatly clarified the matter.

It seems to me, however, that the emphasis on the polar as against the nonpolar structure, as if these had opposite and antagonistic actions, is not clear, and I believe that Dr. Swan emphasized this factor beyond what he actually intended.

In order that a substance should go through a lipoid membrane which is surrounded on both sides by an aqueous face, it has to have affinities both to the water and to the lipoid portion, so that the maximum penetration is obtained by substances which have a balanced degree of polar and nonpolar characteristics. Substances that are wholly polar, like inorganic salts, dextrose or urea, have, as Dr. Cogan and his co-workers have shown, little power of penetration through the corneal epithelium. On the other hand, substances that are wholly lacking in polar groups also have little penetration. Only those substances which combine the two effects are able to get through both faces of this tissue.

That is a characteristic which has been found in a great many other organs, and perhaps the most classic work on these problems was done by Amberson and Hoeber, who studied the penetration of various substances through the salivary glands and found that, starting with a substance that is wholly nonpolar, one can increase its penetrating power by adding polar groups and starting with a substance that is wholly polar, one can enhance its penetrating character by adding nonpolar groups. Finally, if substances of a similarly balanced structure are compared, molecular size plays an important role.

I should like to ask Dr. Swan whether this interpretation of his data is correct.

DR. KENNETH C. SWAN, Iowa City: It is correct. I am sorry if I gave the impression that polar and nonpolar structures are two separate entities. They are not. In the group of naphthalene derivatives studied, the middle series of compounds had both characteristics, and I appreciate what Dr. Friedenwald added to the statement in clarifying that fact.

DR. SANFORD R. GIFFORD, Chicago: What conclusions can be drawn as to the penetration of alkaloids not only into the cornea but into the aqueous in various mediums?

DR. KENNETH C. SWAN, Iowa City: That, I think, we shall have answered in the second paper. I mentioned the preliminary experiments. We found that the distribution of compounds in the aqueous was not a direct index of penetration across the epithelium. For instance, in the living eye the blood supply to the iris, the activity of the iris and the distribution of the drug in the lens and in the vitreous, as well as in the anterior part of the sclera, complicate matters. For that reason, we separate the two problems, and the second phase of our work is concerned with the factors determining the concentration of drugs in the aqueous as compared with the cornea and other tissue.

DR. CLYDE A. CLAPP, Baltimore: It has recently been stated that drops instilled on the upper surface of the cornea are absorbed more readily than drops placed on the lower conjunctival tract. Does the essayists' work clarify that statement at all?

DR. KENNETH C. SWAN, Iowa City: I think that point was clarified by Laquer in about 1876. He demonstrated that absorption from the conjunctival cul-de-sac is primarily through the cornea as contrasted to the conjunctiva. Later on, Antonifon repeated Laquer's work, blocking off the conjunctiva (I have forgotten the name of the material, but I think it was sodium chloride) so that only the cornea was exposed. As I recall, he found that the ratio was 9 to 1 in favor of the cornea (that is, 90 per cent of the material was transported by the cornea), so that instilling a drug at the top of the cornea would bring more of the drug into contact with the corneal surface.

Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis in Premature Infants. III. Studies in Development and Involution of Hyaloid Artery and Tunica Vasculosa Lentis. DR. T. L. TERRY, Boston.

Study of fibroblastic overgrowth of tunica vasculosa lentis in infants born prematurely has led to interest in the development and regression of the hyaloid artery and tunica vasculosa lentis system. This vascular system had been studied in serial sections of eyes from human fetuses of various ages. Injections of the system with india ink and other substances have been made in fetal and postnatal rats, cats, pigs and pouch young opossums. The systems in a few nonviable human fetuses have also been injected. A study has been made of the eyes of premature infants to determine the normal status of tunica vasculosa lentis after premature birth.

From this variegated material many interesting observations have been made. In disagreement with Mann's findings, the vessels of the

pupillocapsullary portion of tunica vasculosa lentis at early stages have no tendency to avoid the center of the pupillary area. Suggestions of parallelism between the main branches of the hyaloid artery and the Y suture of the lens are found in some cases. Simplification and reduction in number of the vascular pattern in the region of the equator correspond to the valleys of the ciliary processes, which must indicate that at one stage the ciliary processes become more simple or the vessels have to adapt themselves to relatively few channels to reach the anterior surface of the lens. Instances of a double hyaloid artery have been observed. Although there appears to be no reason to doubt that the hyaloid artery always carries blood toward the lens, it is probable that the pupillocapsullary portion of the hyaloid system has both arterial and venous supply in common with the mesodermal portion of the developing iris and therefore should be able to maintain patency even after the hyaloid artery is closed.

Factors causing first the development and later the regression of this vascular tree were discussed hypothetically. When the vascular system develops, the lens appears disproportionately large and is growing more rapidly than the rest of the eye. As the eye grows the hyaloid artery must grow or become stretched. As the need for a tremendous blood supply decreases, the stretching ends in breaking of the connection, usually, but not invariably, near the nerve head. Instances of remains of the hyaloid artery reaching to the back of the lens testify to such variations. Disappearance of the annular vessel and later growth of the iris make the venous drainage of the vascular tunic more tortuous and may tend to be somewhat of a stretching factor as well as to offer a lessening of pressure difference through increased friction incident to the lengthening of the vessels. According to Thoma's law, vessels are kept open and grow because of the difference in blood pressure, disappearing when these differences have become considerably less. At early stages no aqueous is available to give nourishment to the lens. Development of aqueous gives another source of nutrition, so that blood vessels are less necessary. Striking shallowness of the anterior chamber, distortion of the ciliary processes and failure of hydrophthalmos to develop when glaucoma does occur in patients with the fibroplasia point to an abnormally meager production of aqueous.

Gonioscopic Studies on the Canal of Schlemm. Dr. Peter C. Kronfeld, Dr. H. Isabelle McGarry and Dr. Homer E. Smith, Chicago.

The gonioscopic phenomenon, originally described by Salzmann, of a blood-filled canal of Schlemm is observed not infrequently during routine examinations of nonglaucomatous eyes. The phenomenon is inconstant, difficult to reproduce and in many instances probably related to excessive squeezing on the part of the patient during the insertion of a contact lens or to pressure of this lens on prominent anterior ciliary veins.

The present study deals with the constant and regular phenomenon of the appearance of blood in the canal of Schlemm in nonglaucomatous eyes following minimal to complete aspirations of aqueous.

After complete emptying of the anterior chamber the phenomenon is visible as soon as sufficient fluid has been reformed to permit gonio-

scopic examination, and it persists until the tension has risen to a tonometric reading of about 15 mm. (Schiøtz). During this period of hypotony the canal appears as a scarlet to purple-red band situated in the depth of the posterior two thirds of the trabecular area. The band measures from one to two thirds of the trabecular area in width. It is at first fairly uniform in density but breaks up into segments, or islands, toward the end of the hypotonic phase. Gonioscopically no leakage of blood from the canal of Schlemm into the anterior chamber can be observed.

In glaucomatous eyes this gonioscopic phenomenon presents strikingly different features, the study of which opens up a new avenue of approach for the investigation of the mechanism in the various forms of glaucoma.

DISCUSSION

DR. MANUEL URIBE TRONCOSO, New York: I think that gonioscopy not only is now an interesting method of practical examination of the eye but has been a means of promoting consideration of and research in the structure of the angle.

Dr. Kronfeld's paper can be studied from two points of view, the physiologic and the pathologic. I am glad that his studies confirmed what I said about the normal contents of the Schlemm canal and the fact that under pathologic conditions of pressure the canal fills up with blood. But he goes a step farther, and he has been able to trace some small pores in the trabeculum from which he saw blood leaking out. This is interesting because it brings one back to the old conception that the inner wall of the Schlemm canal is not a continuous membrane but has some stomas, or apertures, through which aqueous flows in. Whether the apertures are preformed channels or are simply due to the rupture of the endothelial wall of the canal by the increase in inside pressure by the blood, I cannot tell, but gonioscopy may provide the answer.

From the second point of view, the pathologic, Dr. Kronfeld's paper is interesting, because it suggests a means of finding out whether the Schlemm canal is closed in glaucoma. In primary congestive glaucoma, acute and chronic, the angle is almost always closed by a synechia, partial or total, and one cannot use the method of Dr. Kronfeld, because the canal is covered by the synechia, at least partially. On the other hand, in cases of wide angle glaucoma, which is known as chronic simple glaucoma, one may be in doubt as to the condition of the Schlemm canal. By puncturing the anterior chamber and finding out whether the canal fills up with blood one can determine whether it is partially or entirely closed. The method does not empty the anterior chamber entirely. A small amount of fluid remains, and then gonioscopy is done again. If there is some blood in the canal, if it is partially filled, then the canal is only partially open.

DR. JONAS FRIEDENWALD, Baltimore: I should like to report on some experiments performed by Dr. Sholz and myself in which we tried to throw light on the presence or absence of blood in the Schlemm canal of animals under normal conditions.

We used cats, dogs, rabbits and guinea pigs, and in order to avoid loss of blood from the canal during the process of enucleation and fixation, we froze the eye with liquid air without any previous local manipu-

lation. The front segment was sawed off and fixed by being placed in alcohol at a temperature far below zero. The sections then revealed the vessel which formed the base of the experiments.

In a number of animals we punctured the anterior chamber before freezing the segment, and we then regularly found the vessel filled with blood.

These experiments, I think, have a bearing on and completely support Dr. Kronfeld's findings, and they also suggest that the anatomic differences between the lower animals and the primates described by Dr. Troncoso have less functional significance than might be supposed.

I should like to ask Dr. Kronfeld whether he has done repeated punctures when the bleeding phenomena was present, allowing a sufficient interval so that any mechanically ruptured pores would have an opportunity to heal. I think that experiments comprising such punctures might throw light on whether the pores are normally present anatomic structures or merely the result of rupture from mechanical manipulation.

DR. K. W. ASCHER, Cincinnati: There are so many valuable facts in Dr. Kronfeld's paper that every chapter would warrant an extensive discussion. I should like to mention only a few points, and I ask Dr. Kronfeld to allow me to project once more the slide showing Salzmann's picture of the canal of Schlemm. Then I should like to show my slide, no. 6, of the aqueous veins.

(A slide was shown.) I should like to call attention to the fact that in the canal of Schlemm the distribution of blood is apparently similar to the distribution of blood in the aqueous veins. Whenever one looks at the picture of Salzmann showing the canal of Schlemm, one wants to doubt whether this (indicating) border of the blood band is really coincident with the border of the canal. I suppose that the canal of Schlemm reaches up to here (indicating) and that this whole feature might be the canal filled to one half with blood and to one half with aqueous humor, according to the findings in the aqueous veins.

I am glad to find confirmation of this opinion in some words of Dr. Kronfeld, who said that in certain cases the ratio of blood to aqueous humor is changing. It may be one third, if I am right, or one half or even less than one third in a glaucomatous eye. This means that the level of blood in the canal of Schlemm may change. In aqueous veins the distribution of blood in aqueous humor is not always the same. There is not always the stratification visible which appears in this slide of the canal of Schlemm, but if the stratification is visible, one may observe changes in the ratio of blood-aqueous veins, too.

(A slide was shown.) This is an aqueous vein (indicating). Here clear fluid comes out of the region, and here it is added to the blood which is present in the conductive vein. A similar picture is here. One always sees the stratification, which is not dependent on gravity, because one sees for instance here, the blood in the upper and the aqueous in the lower half.

In other words, I want to draw attention to this analogy, this parallel. I think that one has to consider the physiologic unity of the whole system of the canal of Schlemm with the so-called collectors. Blood and aqueous humor are present or not, may be present, may be mixed, in the canal of Schlemm in the so-called collectors—and a name I do not like to use is "canal."

One more word about the color of the blood seen by Dr. Kronfeld in the canal of Schlemm. I think the fact that the blood appears to be bright red does not confirm the arterial origin of this blood in the conjunctiva. One sees blood of a bright color, but that does not mean that all the vessels with bright red blood are arteries. I shall not enter a discussion of why this blood shows the bright red color. It may be something in connection with its arterialization in the conjunctival epithelium through the mesoderm. Anyhow, the fact that the spaces are bright red and the presence of bright red blood in the canal of Schlemm do not prove the origin of this blood; it is possible and fairly probable that it comes from the afferent arterioles.

DR. FREDERICK H. VERHOEFF, Boston: I should like to ask Dr. Kronfeld whether the patients knew that the experiments were in the interest of science and that there was a certain risk connected with them. In a good many of the patients on whom he operated apparently the eyes were normal.

I should also like to ask him whether he has had one of these experiments performed on his own eyes.

DR. PETER C. KRONFELD, Chicago: I greatly appreciate Dr. Troncoso's remarks. I should like only to state again that the presence of leakage in some of our cases from the canal into the trabeculum and into the anterior chamber should not be construed as evidence of preexisting open connections between the canal of Schlemm and the anterior chamber. The leakage after the compression experiment occurs only if the pressure during the compression has been very high. After partial aspiration of the anterior chamber, the leakage occurs infrequently, certainly in less than 20 per cent of cases. After complete aspiration of the anterior chamber, leakage occurs in approximately 20 per cent, which would seem to indicate that the leakage occurs more often if the actual trauma to the eye is greater.

Therefore, I should be inclined to think that these experiments confirm the presence of a delicate wall, a delicate separation between the canal of Schlemm and the anterior chamber, and that this delicate wall may break down under the influence of certain traumas. The greater the trauma, the greater is the likelihood of a breakdown.

It is true that this method can be used to find out whether the canal of Schlemm is present in a certain eye. I interpreted Dr. Otto Barkan's last paper on the treatment of hydrophthalmos in that direction. I believe that he could actually see the red band behind the trabeculum and, therefore, demonstrated or proved to himself that a canal of Schlemm was present in the eyes examined.

With regard to Dr. Friedenwald's comment, Dr. Friedenwald was kind enough to tell me about his experiments with Dr. Sholz, and they are mentioned in this paper. I am, of course, glad to know that they confirm our results.

With regard to his question whether we had performed repeated punctures of the anterior chamber in some of the cases with sufficiently long intervals between punctures to allow complete restoration of normal conditions, the longest interval between two punctures was six weeks.

Dr. Ascher's comment, his idea that the picture we showed may represent stratification, that the entire canal may not be filled with

blood and that there may be a lower layer of blood and an upper layer of aqueous, is interesting, and I had not thought of that possibility. There is, however, one thought that comes to my mind. If the canal is filled immediately after compression and one watches the phenomenon of filling while it takes place, one sees that the blood simply rushes in, and it would be difficult to conceive that during this sudden entrance, as the blood really gushes into the canal, only a portion of the canal should become filled. The width of the area that becomes filled under those conditions is the same as that after partial aspiration of the anterior chamber in most cases. Therefore, just on the basis of these observations, I am inclined to think that these pictures represent complete filling of the canal, and not stratification.

In answer to Dr. Verhoeff, the eyes were not normal. As I stated in the paper, there were clinical conditions of amblyopia, senile cataract, senile macula, degeneration, optic nerve atrophy, and so on, and the patients were told that this was an experimental procedure which might for short periods improve the circulation of blood to the eye.

With regard to Dr. Verhoeff's question whether any of the authors of this paper had undergone the procedure, I am glad to say that two (including myself) had compression of the eyeball with the ophthalmodynamometer performed on their own eyes just to find out how it felt. However, gonioscopic observations were not made. The procedure is slightly painful.

DR. FREDERICK H. VERHOEFF, Boston: Including the puncture of the anterior chamber talked about?

DR. PETER C. KRONFELD: No.

Observations and Experimental Studies on the Physiology of the Ciliary Muscle. DR. ERICH SACHS, Detroit.

The behavior of the ciliary muscle under faradic stimulation has been observed in excised eyes (cat, dog). A phenomenon never before reported was noted and was confirmed by observation of pins thrust radially through the anterior wall of the eyeball and of chalk particles dusted on the ciliary body through a scleral window. As the muscle contracted, the posterior tissue of the ciliary body stretched forward, but the anterior coronal region expanded backward, with a narrow motionless zone separating the two moving regions.

The amplitude, speed and force of contraction at various points along a meridian were measured with a micrometer scale, a stopwatch and an electromagnetic ductor calibrated in milligrams. Except in the fundal area subtending about 50 degrees of the circumference of the eyeball, there was demonstrable forward movement of the choroid along all meridians. Within the nonmoving area of the choroid, no increase in circumferential tension during contraction of the ciliary muscle could be demonstrated.

DISCUSSION

DR. FREDERICK H. VERHOEFF, Boston: How about the question of sympathetic stimulation? Some muscles respond to sympathetic stimulation, and others respond to parasympathetic stimulation. Doesn't this confuse the results?

DR. ERICH SACHS, Detroit: The stimulation was a direct one, applied to the muscle itself in the enucleated eye.

DR. FREDERICK H. VERHOEFF, Boston: It would take in all the muscles, then. I mean, suppose some muscles normally were stimulated by the sympathetic fibers and others were stimulated by the third nerve and in accommodation only those stimulated by the third nerve were used. In Dr. Sach's experiments he stimulated all of them at once?

DR. ERICH SACHS, Detroit: Yes.

DR. FREDERICK H. VERHOEFF, Boston: Of course, if that is true, then the results would be difficult of application to any theory of accommodation.

DR. ERICH SACHS, Detroit: The same experiments have been performed by ganglionic stimulation. The first persons who observed this phenomenon used ganglionic stimulation. They never observed the backward movement. They apparently put the pins just in the neutral zone, or, at least, the pins were not immediately behind the limbus in this region. Not all eyes showed the backward movement. Previous experimenters had not used many eyes.

DR. FREDERICK H. VERHOEFF, Boston: Dr. Sachs has not tried stimulating the nerve in the sympathetic area?

DR. ERICH SACHS, Detroit: Not yet, but I shall do so. The experiments certainly have to be performed also with ganglionic stimulation, which will be the next task.

DR. FREDERICK VERHOEFF, Boston: Does Dr. Sachs think that there are two sets of fibers: fibers innervated only by the third nerve and fibers innervated only by the sympathetic system?

DR. ERICH SACHS, Detroit: That is a difficult question. Personally, I do not think so. I think that, like the iris, the sphincter is relaxed by some sympathicomimetic drugs which have a double action (a sympathetic action, with or without an accompanying negative parasympathetic action, according to the tissue), this taking place in the ciliary muscle. I have to confess that all pharmacologic experiments have failed completely. With the exception of nicotine, as far as I know nobody ever got results by using drugs on the ciliary muscle. I do not know the reason. I dropped acetylcholine on the surface and I injected it into the vitreous, and once I got a very, very slight contraction, which may have been due to the change in p_H. None of the authors of the last century ever considered change of p_H.

Therefore I cannot say anything about stimulation with drugs, especially why it fails absolutely on the exposed ciliary muscle—even use of the strongest drugs in potent combinations.

DR. FREDERICK VERHOEFF, Boston: It does not make any difference on which side one applies the drug?

DR. ERICH SACHS, Detroit: From the inside or the outside, or injected into the vitreous immediately below, the drug did not produce any reaction. The preparations were observed for fifteen or twenty minutes. By means of a chart method, I would have seen even movements of 76 microns and less.

DR. FRANCIS H. ADLER, Philadelphia: Did Dr. Sachs get any dilatation or contraction of the pupil when he stimulated the ciliary region?

DR. ERICH SACHS, Detroit: Definitely: in cats, dilatation; in dogs, contraction. The animals react oppositely.

DR. FREDERICK VERHOEFF, Boston: In round pupils has Dr. Sachs found an exactly uniform reaction?

DR. ERICH SACHS, Detroit: The stimulation is a local one, and the dog's pupil always becomes oval. The dog is peculiar, because the stimulation should dilate the pupil.

DR. FREDERICK VERHOEFF, Boston: Can Dr. Sachs harmonize his theory with the Helmholtz theory of accommodation?

DR. ERICH SACHS, Detroit: Yes, absolutely I can. As soon as I assume that the backward movement has nothing to do with the relaxation of the main zonular fibers, I cannot see any mechanical influence originating from it.

DR. FREDERICK VERHOEFF, Boston: If that is the only kind of movement one gets, how does one relax the zonule?

DR. ERICH SACHS, Detroit: I do not get only the backward movement. The backward movement extends over the coronal part of the ciliary body, then comes the neutral zone, and from there through the larger part of the ciliary body and the coronoid the tissue moves forward in the well known way. I would assume, certainly, that that is the main working part of the uvea. So this hypothesis does not contradict Helmholtz' theory of relaxation of the zonular fibers. Whether this backward movement influences the posterior zonular fibers or those which travel away from the more anterior part of the ciliary muscle, I do not know. It is difficult to see through all the complicated mechanical possibilities. Until I can make observations on a primate, I do not care to advance any theory.

Sulfadiazine Iontophoresis for Bacillus Pyocyaneus Infection of Rabbit Cornea. DR. LUDWIG VON SALLMANN, New York.

The concentrations of the newer sulfonamide compounds (sulfapyridine [2-(paraaminobenzenesulfonamido)-pyridine], sulfathiazole [2-(paraaminobenzenesulfonamido)-thiazole] and sulfadiazine [2-(paraaminobenzenesulfonamido)-pyrimidine]) which enter cornea and aqueous by local administration can be considerably increased by the iontophoretic application of their sodium salts. J. Boyd demonstrated such an increase using sodium sulfathiazole, and my experiments with sodium sulfapyridine and sulfadiazine gave similar results.

On the basis of these findings iontophoretic treatment of the most invasive corneal infection (that due to Bacillus pyocyaneus) of the rabbit was initiated. The progression of the keratitis was checked in approximately half of the experiments eighteen hours after inoculation, sulfadiazine being used iontophoretically alone. Good results were obtained in most instances when local treatment was combined with the feeding of comparatively small doses of the drug. The combined treatment overcame the progression twenty-four hours after inoculation. The effect of the iontophoretic application is definitely superior to that of the local use of sulfadiazine powder. No damage to the corneal epithelium due to iontophoresis could be observed.

Aqueous veins: Physiologic Importance of Visible Elimination of Intraocular Fluid. DR. K. W. ASCHER, Cincinnati.

Aqueous veins are blood-vessel-like pathways that are biomicroscopically visible. They contain a clear fluid or diluted blood and are intercalated, probably via Schlemm's canal, between the intraocular fluid on one side and conjunctival and subconjunctival veins on the other.

Priority may be claimed for the observation of the entrance and presence of intraocular fluid in circulating blood. The fact of a continuous outflow of intraocular fluid, according to Leber's theory, was not obvious prior to the knowledge of these visible connections.

Only one counterpart of this elimination of fluid more or less mixed with blood seems to exist in nature. Every contraction of the posterior lymph heart of the frog forces clear fluid into the renal vessels.

The anatomic substrata for the aqueous veins are the anastomosing intrascleral vessels, which, according to Friedenwald, occasionally send branches to the episcleral vessels at the limbus. Therefore, the origin of aqueous veins is found in or near the limbus, often with a U-like arch, one limb of which emerges from the limbal tissue. On considering the different figures available in the literature for the amount and size of the venous outlets of Schlemm's canal and for the speed of movement in conjunctival veins, one arrives at an approximate agreement between the volume possibly eliminated by aqueous veins and the amount suggested by Friedenwald and Pierce.

Aqueous veins are to be recognized by their origin, course and emptying; by their content of diluted blood or even of colorless fluid, and by the response to compression of the recipient vessel. Stratification is sometimes present and will disappear on slight compression of the recipient vein. Either of two phenomena then may occur: (1) the red blood cells are forced back into the aqueous vein, in a direction opposite to the original current, or (2) the red cells are expelled out of the recipient vessel until the whole structure looks like a colorless glass rod embedded in porcelain: the glass rod phenomenon.

Stratification paralleling the vessel walls has been observed in the mesenterium and in the tongue of the frog, but the explanation of this striation is quite a different one.

In the Cincinnati Eye Clinic, no patient with primary compensated glaucoma showed the glass rod phenomenon, but the number of eyes investigated so far is too small for any decisive conclusion. In some eyes with secondary glaucoma, the glass rod phenomenon was present.

In aqueous veins, in their tributaries and in their recipient vessels, borderlines paralleling the vessel diameters and separating sanguineous from colorless fluid may be formed. Rhythmic pulsation may occur in the borderline. The expulsion of red blood corpuscles takes place synchronously with the acme of the radial pulse.

Sometimes a rhythmic influx of red blood cell waves arrives in the interval between two pulse beats.

Respiration may produce changes in the red blood corpuscle content. Movements of the lids, changes between light and dark and use of miotics, mydriatics and other drugs may influence the content of an aqueous vein.

DISCUSSION

DR. FREDERICK H. VERHOEFF, Boston: I should like to ask Dr. Ascher whether there is any significance in the appearance of these veins in glaucomatous and normal eyes, and in different types of glaucoma, too, for instance in acute glaucoma without congestion and simple chronic glaucoma, and whether the veins look the same as in normal eyes.

DR. K. W. ASCHER, Cincinnati: The number of glaucomatous eyes is not large enough for the drawing of clear and complete conclusions, but I can say that the occurrence of aqueous veins is not lower in glaucomatous eyes than it is in normal eyes, or, I had better say, in eyes without abnormal intraocular pressure. However, one can see that any congestion, whether it is due to glaucoma or inflammation, interferes with the visibility of aqueous veins. Trauma, puncture of the chamber, contusion, keratitis or anything which tends to increase the red cells in the conjunctival vessels conceals the appearance of aqueous veins, and that fact may be in accordance with the observations of Dr. Kronfeld. He observed that when one punctures the eye and part or all of the aqueous humor escapes, then a large amount of blood suddenly enters the canal of Schlemm. The same process occurs in aqueous veins: When the pressure of the aqueous phase is diminished, blood enters and no more stratification is visible, for stratification is due only to the simultaneous presence of the aqueous and the sanguineous phase. When the intravascular pressure is changed, in a moment all stratification is destroyed.

DR. FREDERICK H. VERHOEFF, Boston: But if one had an infiltration angle and high blood pressure, the aqueous veins would be distended and the clear stream would be longer, would it not?

DR. K. W. ASCHER, Cincinnati: I do not know.

DR. FREDERICK H. VERHOEFF, Boston: Dr. Ascher has not observed an effect?

DR. K. W. ASCHER, Cincinnati: I have, but it is not clear. My observations have not been extensive enough for me to make a definite answer.

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

ALFRED COWAN, M.D., *Chairman*

WARREN S. REESE, M.D., *Secretary*

Dec. 17, 1942

Edward Jackson, A Founder of the Section. DR. BURTON CHANCE.

This article will be published in full in the *American Journal of Ophthalmology*.

Luther Crouse Peter, M.D. DR. EDMUND B. SPAETH.

This article was published in full in the January issue of the ARCHIVES, page 143.

William Toy Shoemaker, M.D. DR. WILLIAM ZENTMAYER.

This article was published in full in the February issue of the ARCHIVES, page 307.

Lipaemia Retinalis. DR. M. LUTHER KAUFFMAN.

Two patients with lipaemia retinalis were presented, both showing interesting and somewhat unusual characteristics. The first did not have diabetes and is the third such patient to be reported on in the literature. He had suffered from chronic alcoholism for about two years and had had attacks of acute gastritis and vascular hypertension. The second patient had changes in the walls of the retinal vessels and severe retinosis complicating her diabetes.

When first seen, neither patient was in coma. If either patient had acidosis it was not revealed by test of the carbon dioxide–combining power of the blood or the urinalysis; the p_H of the blood was not determined.

The visibility of hyperlipemia in the retinal blood vessels depends to some extent on the lipid content of the blood. I suggest that another factor may be the size of the lipid particles, which become larger in the presence of chemical or electrolytic imbalance. The increase in the size of the particles causes the lipids to be easily visualized through the vessel walls. The particles in an emulsion tend to coalesce, and they become larger in anything but the optimum medium for that emulsion.

DISCUSSION

DR. EUNICE LEB. STOCKWELL: I should like to report on a patient with lipaemia retinalis seen several months ago. He was 41 years old and when admitted to the hospital had a typical history of diabetes mellitus of four months' duration. Insulin had not been administered. On the day of his admission the concentration of sugar in the blood was 301 mg. and that of cholesterol 1,456 mg. per hundred cubic centimeters. The carbon dioxide volume was 60 per cent. Examination of the fundi revealed the typical picture of lipaemia retinalis. The veins were full and were cream colored except at their terminal branches, where they were white. The arteries were flat and ribbon-like and simulated the veins in size and color.

The patient was given insulin, and the next day the typical picture of lipaemia retinalis had disappeared. Although the veins and arteries were still slightly pale and the cholesterol content in the blood was 1,401 mg., the vessels had returned to their normal color.

DR. ALEXANDER G. FEWELL: Dr. Kauffman is to be congratulated on detecting lipaemia retinalis in a nondiabetic person. I have seen only 2 patients with lipaemia retinalis. I think the condition is much more common than would appear from the literature. The case reported by Dr. Stockwell was a typical case of lipaemia retinalis, but the retinal picture entirely disappeared within forty-eight hours.

Little has been added to Heyl's original ophthalmologic observation, made in 1886. With 2 exceptions, all patients previously reported on have been diabetic. One exception was the patient reported on by Wagner in 1922, a boy 9 years of age, who had undergone radium treatment for leukemia. The other was a poorly nourished child, 1 year old, with associated xanthomatosis and enlargement of the spleen. Nearly all of the patients reported on have had associated acidosis, and many have had xanthomatosis. The acidosis is usually severe and of short duration, but it may extend over a long period and be comparatively mild, as in the last patient reported on by McKee. In only a few instances has there been a careful chemical analysis of the blood with studies of the various blood lipids. In general terms, I may state that lipaemia retinalis appears when the value for blood fat rises above 3.5 per cent and disappears when it falls below 2.5 per cent.

It has been suggested before that the manifestations of lipaemia retinalis are due to some condition other than an excessive amount of fat in the blood. This must be true, as a number of cases have been reported in which the fat content of the blood was high but lipaemia retinalis was not present.

Before the discovery of insulin, practically all diabetic patients in whom lipaemia retinalis developed died in diabetic coma, but now, with insulin, such patients may live for many years.

DR. I. S. TASSMAN: I should like to ask Dr. Kauffman if he knows of any relationship between lipaemia retinalis and the white cell count, especially since a patient reported on by Wagner had leukemia.

The appearance of lipaemia retinalis with xanthomatosis is understandable, because usually this condition is associated with diabetes, particularly when it occurs in a young child in the form of the Schüller-Christian disease, which is a disease of the lipoid metabolism.

DR. M. LUTHER KAUFFMAN: I thank the discussers for their contributions. Concerning acidosis, I should like to point out that even though the urinalysis and all other tests give normal results, it is, according to chemists, impossible to say that acidosis does not exist unless the p_H of the blood is determined. The acidosis is called an uncompensated acidosis.

As Dr. Stockwell pointed out, lipaemia retinalis may be much more common than the literature indicates. The way to discover it is to make an ophthalmologic examination of every patient admitted to the medical service of the hospital.

The ratio of phospholipids to total fat is to be considered as causing hyperlipemia to become visible in the retinal vessels. It may also have an effect on the electrolytic balance. Chemists point out that any change in the electrolytic balance will have a tendency to make the fat particles coalesce.

My male patient had a leukocyte count below 9,000 at all times. The girl's count ranged from 8,000 to 16,000, but she had frequent infections. I do not believe that the leukocyte count is a factor in hyperlipemia.

Unusual Case of Birth Injury of the Eye. DR. F. H. ADLER and DR. E. GERARD SMITH.

The case presented was that of a 33 year old physician. At birth he had incurred an injury evidenced by a large depression over the left

frontal arc. In 1931 refraction revealed that vision in each eye was 20/20 with a correction for the right eye of — 2.50 D. sph. ⌒ — 0.50 D. cyl., axis 60, and for the left of — 3.50 D. sph. ⌒ — 2.25 D. cyl., axis 180. In 1935 the correction which brought the vision to 20/20 in each eye was — 2.50 D. sph. ⌒ — 0.75 D. cyl., axis 50, for the right eye and — 2.75 D. sph. ⌒ — 2.75 D. cyl., axis 165, for the left.

On reexamination in 1938 the right eye was found to be about the same and the left to require a correction of — 1.00 D. sph. ⌒ — 2.75 D. cyl., axis 166. Four years later refraction of the right eye showed little change but that of the left eye a change of cylinder to — 3.25 D., axis 166. When the patient was last examined, in 1942, the right eye again showed little change. Refraction of the left eye indicated a correction of + 2.25 D. sph. ⌒ — 3.50 D. cyl., axis 170. This represents over a period of ten years a total change of 5.75 D.

Tests of ocular motility showed a left hypertropia with fixation with the left eye. The right eye turned down and in, the patient suppressing the vision in this eye. Owing to facial asymmetry, the left eye was 5 mm. higher than the right. Rotation was full in all directions in each eye save outward in the left, where there was some limitation of movement. The right fissure was slightly wider than the left. The tension taken with a Schiøtz tonometer was 20 mm. of mercury in the right eye and zero in the left eye.

Slit lamp examination of the right eye showed a few pigmented and nonpigmented deposits on the corneal endothelium but otherwise revealed nothing abnormal. The left eye showed severe chemosis of the lower bulbar conjunctiva, the swelling filling the whole lower cul-de-sac. There were no other signs of inflammation. There was considerable pigment on the anterior lens capsule, probably congenital in origin.

Ophthalmoscopic examination revealed that the right fundus was normal. Ophthalmoscopic examination of the left fundus showed slightly indefinite margins at the upper and lower poles of the disk. There were some reflexes in the retina which were suggestive of folds and which may have been due to an old retinal detachment.

We believed that the picture might have a rational explanation. The globe might have been ruptured at birth. The rupture had probably healed but might have left a fistula through which aqueous was escaping into the conjunctiva and retroretinal spaces, which would have accounted for the chemosis of the conjunctiva and possibly a forward displacement of the retina. The latter was suggested by the change in refraction.

DISCUSSION

DR. F. H. ADLER: I am sure Dr. Smith and I, and our obliging patient, would welcome any suggestion that would differ from this explanation. I have not been able to find in the literature a case that duplicates this, and the only possible explanation we have at present is what Dr. Smith has stated. The patient's tension in the left eye was zero as measured by the tonometer. I have always taught my students, and have read in the literature, that a tension of approximately 25 mm. of mercury is necessary for the maintenance of the optical properties of the eye. This eye had a visual acuity of 6/6 in spite of zero tension.

DR. JAMES S. SHIPMAN: I should like to ask Dr. Smith if he has a record of the patient's tension at the time of the first refraction.

DR. H. MAXWELL LANGDON: Is it not remarkable that this patient's condition remained quiescent for a number of years? As I understand it, about ten years ago peculiarities began to develop in the eye, and the patient is now 34 years of age. What happened to produce this peculiar series of changes? Did anything happen that could have caused an opening of a fistula?

I am not suggesting the presence of a fistula, but I am wondering what caused the drainage to start. Could the pressure on the globe while the tension was being taken with the fingers have caused the apparent leakage of aqueous?

DR. ALFRED COWAN: It does seem remarkable that the condition has progressed as described. Does not such progress seem unusual for an ordinary birth injury? In my experience, birth injuries clear up to a remarkable degree, to a much greater extent than would similar injuries incurred by older persons. So the condition described, if it really is due to a birth injury, is unusual in that it has become progressively worse.

DR. E. GERARD SMITH: With regard to Dr. Shipman's question about the tension, I got in touch with the ophthalmologists who had examined the patient previously, and they told me that his tension was normal when they examined him.

In answer to Dr. Langdon's question about injury to the globe when the tension was being taken with the fingers, as far as I know there was none. The patient believes that the chemosis below the cornea has always been present, to a greater or less extent.

Purtscher's Angiopathy Traumatica Retinae. DR. EDMUND B. SPAETH.

Two cases of Purtscher's disease were reported, one in abstract and the other in detail as to its clinical course.

The literature relative to this condition was discussed, and it was stated that the cause of the angiopathy is still not satisfactorily explained. It was declared that the possibility of fat embolism's being the cause for the retinal changes must be seriously considered.

DISCUSSION

DR. JAMES S. SHIPMAN: This condition is not a recent discovery, having been described by Purtscher in 1910 in the case of a head injury. Even earlier than that, in 1900, Neck noted such fundus changes after compression or crush injuries of the chest. However, most of the literature on the subject is of European origin, and only in the past several years has the subject engaged the interest of American ophthalmologists. In a paper read before the American Ophthalmological Society (Traumatic Retinal Angiopathy, ARCH. OPHTH. **23**: 351-358 [Sept.] 1939), A. J. Bedell reviewed the literature, in which he found 40 cases, and added 3 cases of his own.

In addition to "Purtscher's disease," the condition has been called "traumatic retinal angiopathy," "lymphorrhagia retinae" and, most recently, "retinal teletraumatism." A. Knapp (Medical Ophthalmology,

Philadelphia, P. Blakiston's Son & Co., 1918), described the ophthalmoscopic picture although the disease was given no definite name at that time. More modern textbooks include it under one of the headings mentioned.

The usual history is of rather marked loss of vision in one or both eyes following an injury of the head, a compression injury of the chest or abdomen or fractures of the vertebrae. The visual disturbance appears either immediately after the accident or within a few days.

Externally, small subconjunctival hemorrhages are often present, together with ecchymoses of the eyelids and face, as well as discoloration of the neck, chest and upper extremities. Direct injury to the eye is not evident, such as laceration, nor is there any history of such injury.

Ophthalmoscopic examination reveals fairly typical fundus changes. Essentially, these are hemorrhages, exudates, edema and dilatation of the retinal veins with constriction of the arteries. Pallor of the disk may also be present, but more often this develops later, when, in some cases, secondary atrophy of the optic nerve ensues. Whiteness of the macular region has also been recorded as a late finding.

The hemorrhages may be small or massive, but usually they are the latter. They may be flame shaped or round. Most often they are found in the superficial layers of the retina, but a number of cases of hemorrhages in the vitreous have been recorded. Stokes described a case in which there was such a massive hemorrhage in the macula that the macula had the appearance of "an island in a lake of blood." In addition, there was in this case a round hemorrhage in the fovea.

The edema and the exudates may be described together, these terms being ill defined by the various authors, and in some instances, as in Bedell's paper, are used interchangeably. This is best shown by descriptions such as "the entire posterior pole was an immense milky white swelling covering the disc and retinal vessels" (Bedell); "a white, cloud-like plaque near the disc" (Bedell); "many discrete, elevated, whitish areas with round edges, some confluent, resembling cotton wool, and found along the superior and inferior temporal vessels" (Stokes). There may also be, as in the case presented by J. W. Smith, "a diffuse dense cloud or veil in the posterior vitreous which entirely obscured the fundus and which was considered secondary to the retinal pathology."

The changes in the caliber of the blood vessels, i. e., the constriction of the arteries and dilatation of the veins, are similar to those seen in thrombosis of the central retinal vein. It may be added here that the exudates are often found along the course of the vessels, and hemorrhages when small are apt to be seen along the retinal veins.

Secondary atrophy of the optic nerve is not a constant finding. A great many of the cases reported have been followed for only a short time. However, Bedell had the opportunity to observe a case fifteen years after he had made the diagnosis of traumatic retinal angiopathy. The disk in this instance was waxy pale and the vision markedly reduced, as one would expect.

The mechanism by which the hemorrhages and exudates are produced is not entirely known. Purtscher's theory was that an injury to the head induced compression of the spine in its longitudinal axis, which, in turn, produced increased intracranial pressure. This pressure forced the spinal fluid through the intervaginal space into the nerve head

and along the retinal vessels, so that it extravasated into the retinal tissue through the ruptured perivascular lymph spaces. However, since the intervaginal space is not a true cavity, this theory is hard to accept. Friedenwald stated the belief, as did Urbanek and Loewenstein, that the changes are due to fat emboli. If this is true, it would seem that the disease should result oftener from fractures of the long bones. Experimentally, Willers trephined the skulls of rabbits and found that the brain could be made to bulge through the hole when pressure was applied to the thorax or abdomen. Each of these theories partially explains the pathologic physiology; no one of them completely explains it.

There has been only 1 case in which histologic sections of the eye were examined microscopically. This was reported by Savitsky and Gross in December 1935 before the New York Neurological Society. They found "round structures within the retinal layers, more in the superficial, which reacted to the stains for fat." There was a division of opinion as to the clinical diagnosis, several ophthalmologists considering retinitis albescens to be the true diagnosis rather than traumatic retinal angiopathy. For this reason it would seem unwise to accept the pathologic picture described as the usual one or as pathognomonic of the condition under discussion.

In none of the reports was any specific treatment suggested; treatment was not even mentioned. Presumably potassium iodide administered internally might be used with good effect.

The prognosis is variable. In a number of cases there has been a return to normal vision, despite rather extensive retinal hemorrhages, exudates and edema. However, secondary atrophy of the optic nerve is always a threat in cases of severe involvement, and in others there has been reported permanent damage in the macular region consisting of fine dots and scattered pigment.

Dr. Edmund B. Spaeth: I uncovered fifty-one relevant references, and these included some 70 cases. In regard to fat emboli and the question which Dr. Shipman raised, is it possible that these instances (cases of frank fat emboli as seen in association with damage to the cerebral cortex) are more likely the result of crushing injuries than otherwise? Injuries to the pelvis are not uncommonly followed by emboli and distant infarcts.

I do not believe that the histologic report mentioned by Dr. Shipman was one of angiopathy traumatica retinae, and I hesitate to consider it as such.